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Biomechanical Analysis of Monolithic Ceramics in Maxillary Lateral Incisor Agenesis Rehabilitation

Maria João Azevedo de Oliveira Calheiros-Lobo

Tese conducente ao Grau de Doutor em Ciências Biomédicas

Gandra, janeiro de 2024

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Trabalho realizado sob a Orientação e Coorientação

Professora Doutora Teresa Maria da Costa Pinho
Professor Doutor Lucas Filipe Martins da Silva

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Dedication

To **Mafalda**, **Joana**, and **Francisca**, the soul of my existence.

To **João Mário,** the father and hero, responsible for my mental restlessness and constant search for knowledge through his example, talks, incredible library, and mainly his fellowship (in memoriam).

To Hilda, an example of a woman, mother, and doctor, always smiling, who inspired me and made me want to help others.

To **João** and **Nuno,** brothers and companions for a lifetime.

To **Zé**, acquired sister for whom I have no defects.

To **Américo**, companion and friend.

To **Sandra**, my right hand, always there for professional and personal issues.

To **ALL** of my growing family.

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ABSTRACT

Treatment planning for replacing a missing maxillary lateral incisor must consider and evaluate esthetic expectations, potential ongoing growth of the patient, and well-coordinated interdisciplinary management. Ideally, a single-retainer resin-bonded bridge would be a valuable treatment modality, with highly predictable and esthetic results in cases of complementary rehabilitation after orthodontic treatment in cases of maxillary lateral incisor agenesis (MLIA) treated with space opening, especially in growing juvenile patients.

Among esthetic materials, yttria-partially stabilized zirconia has better mechanical properties and superior resistance to fracture than other dental ceramics; however, despite investigations, the bonding mechanism between zirconia and veneering ceramics remains poorly understood, with chipping and debonding. To overcome this, strategies have been proposed for adhering computer-aided design/computer-aided manufacturing (CAD/CAM) ceramic parts to a CAD/CAM-zirconia framework without manual steps or a full-contour zirconia resin-bonded bridge. However, effective and durable adhesion to dental structures remains controversial. There are tougher and more user-friendly materials, including zirconia-infiltrated lithium disilicate and polymer-infiltrated ceramic networks, with easier clinical protocols.

Adhesive restorations such as resin-bonded bridges (RBBs) rely on bonding systems and resin cement to form a micromechanical bond with the tooth, although chemical interactions may occur between functional monomers and some tooth components with potential benefits. The enamel varies in thickness, has a high modulus of elasticity, high compressive strength, and low tensile strength, and protects dentin against masticatory forces. If treated with phosphoric acid, it can be infiltrated with a resin material to produce a micromechanical bond. Bond strength tests to assess the adhesive strength of RBBs to the tooth are important because thermal, mechanical, and passive hydrolysis can occur in the mouth, weakening rehabilitation materials. As the base adherend to mechanical tests, natural teeth, in addition to ethical constraints, may induce results bias due to heterogeneity inherent to biological diversity.

Modifications to adhesive protocols and alternative designs for tooth preparation and resin-adhered bridges should be developed to propel new minimally invasive restorative treatments, and a suitable combination of surface treatment and adhesive cementation systems, particularly for zirconia-based resin-bonded bridges (RBBs), requires a standardized protocol that provides a more efficient and predictable bonding effect.

This work aimed to find the best RBB, in terms of material and ease of use in the office, as a definitive or interim option, in clinical situations of MLIA treated with orthodontic space opening. Several combinations of CAD-CAM restorative materials and adhesive luting cement were assessed by shear bond strength tests, mode of failure, and surface energy measurements. Parallelly, an artificial base adherend was searched as an alternative substrate to natural teeth to be used as a standard substrate for shear bond strength tests in the future.

Keywords: CAD-CAM monolithic ceramics, maxillary lateral incisor agenesis, rehabilitation, adhesive cementation, adherend, resin-bonded bridges

RESUMO

O planeamento do tratamento para a substituição de um incisivo lateral maxilar ausente deve considerar e avaliar as expectativas estéticas e o potencial crescimento contínuo do paciente, bem como uma gestão interdisciplinar bem coordenada. Idealmente, uma ponte de apoio único unida com resina seria uma modalidade de tratamento valiosa, com resultados estéticos e previsíveis, como reabilitação complementar após o tratamento ortodôntico de casos de agenesia do incisivo lateral maxilar (MLIA) tratados com abertura de espaço, especialmente em pacientes jovens em crescimento.

Entre os materiais estéticos, a zircónia parcialmente estabilizada com ítria tem melhores propriedades mecânicas e resistência à fratura, superior às outras cerâmicas dentárias. No entanto, apesar das investigações, o mecanismo de ligação entre zircónia e cerâmicas de revestimento permanece mal compreendido, com lascamento e descolagem.

Para superar isso, foram propostas estratégias para a adesão de peças cerâmicas de desenho assistido por computador/fabrico assistido por computador (CAD-CAM) aderidas sobre uma estrutura CAD-CAM em zircónia sem outras etapas manuais que não a colagem, ou peças em cerâmica monolítica. No entanto, a adesão efetiva e duradoura desta cerâmica às estruturas dentárias permanece controversa.

Existem outros materiais cerâmicos tenazes e mais fáceis de usar e entre eles estão a cerâmica de dissilicato de lítio reforçado por zircónia e a rede cerâmica infiltrada por polímero, com protocolos clínicos mais fáceis.

Restaurações adesivas, como pontes aderidas por resina (RBBs), dependem de sistemas adesivos e de cimento resinosos para formar uma ligação micromecânica com o dente, embora interações químicas possam ocorrer entre monômeros funcionais e alguns componentes dentários com potenciais benefícios. O esmalte natural varia em espessura, tem um elevado módulo elástico, elevada resistência compressiva, baixa resistência à tração, e protege a dentina para suportar forças mastigatórias. Se tratado com ácido ortofosfórico, pode ser facilmente infiltrado por material resinoso para produzir uma ligação micromecânica. Os testes de resistência de ligação para avaliar a resistência adesiva das RBBs ao dente são importantes porque a hidrólise térmica, mecânica e passiva pode ocorrer na boca, enfraquecendo os materiais de reabilitação. Como base aderente para testes mecânicos, os dentes naturais, além de restrições éticas, podem induzir viés de resultados devido à heterogeneidade inerente à diversidade biológica.

Modificações nos protocolos adesivos e projetos de desenho alternativos de preparação dentária e das pontes aderidas com resina devem ser desenvolvidos para impulsionar novos tratamentos restauradores minimamente invasivos, e uma combinação adequada de tratamento de superfície e sistemas de cimentação adesiva, particularmente para pontes unidas à resina à base de zircónia (RBBs), requer um protocolo padronizado que forneça um efeito de ligação mais eficiente e previsível.

Este trabalho teve como objetivo encontrar a melhor RBB, em termos de material e facilidade de uso no consultório, como opção definitiva ou provisória, em situações clínicas de MLIA tratadas por abertura de espaço ortodôntico. Várias combinações de materiais restauradores CAD-CAM e cimentos adesivos foram avaliadas por testes de resistência ao cisalhamento, modo de falha e medições de energia superficial. Paralelamente, procurou-se um base aderente artificial para ser utilizado no futuro nos testes de resistência ao cisalhamento, como um substrato padronizado alternativo aos dentes naturais.

Palavras-chave: cerâmica monolítica CAD-CAM, agenesia do incisivo lateral maxilar, reabilitação, cimentação adesiva, aderente, pontes aderidas por resina

ACKNOWLEDGMENTS

This dissertation, a solitary process for any researcher, brings together contributions from several people. Since the beginning of my doctorate, I have had the trust and support of countless people and institutions. Without these contributions, this investigation would not have been possible.

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Finally, my heartfelt thanks go to everyone who contributed to this dissertation and encouraged me intellectually and emotionally.

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List of Abbreviations and Acronymous

μm – micrometer

μTBS – micro-tensile bond strength test

Al_2O_3 – aluminium oxide

Bis-EMA – bisphenol A diglycidyl methacrylate ethoxylated

Bis-GMA – bisphenol A-glycidyl methacrylate

BPA – Bisphenol A

CAD-CAM – Computer-Aided Design/Computer-Aided Manufacturing

CoJet – system for tribochemical silica airborne-particle abrasion

CP – yttria or yttrium oxide cubic phase

FC – feldspathic ceramic

FEA – finite elements analysis

HF+S – hydrofluoric acid followed by silanization

KHF_2 – potassium bifluoride

HT-Z – high translucency zirconia

LS_2 – lithium disilicate

MDP – 10-methactryloyloxydecyl dihydrogen phosphate

MLIA – maxillary lateral incisor agenesis

PICN – polymer infiltrated ceramic network

RBB – ceramic resin bonded bridge

RCT – randomized controlled trials

SARC – self-adhesive cement

SBS – shear bond strength test

SC-R – self-curing resin composite

SE-A – self-etching bonding system

TP – yttria or yttrium oxide tetragonal phase

Y-ZPT – yttria-stabilized zirconia

ZLS – zirconia reinforced lithium disilicate

ZrO_2 – zirconium dioxide

List of Publications

Published in the scope of this thesis

Calheiros-Lobo MJ, Calheiros-Lobo JM, Carbas R, da Silva LFM, Pinho T. A Polymer-Infiltrated Ceramic as Base Adherent in an Experimental Specimen Model to Test the Shear Bond Strength of CAD-CAM Monolithic Ceramics Used in Resin-Bonded Dental Bridges. **Coatings** 2023, 13, 1218. doi:10.3390/coatings13071218 **(Q2)**

Calheiros-Lobo MJ, Calheiros-Lobo M, Pinho T. Esthetic Perception of Different Clinical Situations of Maxillary Lateral Incisor Agenesis According to Populations with Dental and Non-Dental Backgrounds: A Systematic Review and Meta-Analysis. **Dent J** 2023, 11, 105. Doi:10.3390/dj11040105 (**Q2**)

Calheiros-Lobo MJ, Vieira T, Carbas R, da Silva LFM, Pinho T. Effectiveness of Self-Adhesive Resin Luting Cement in CAD-CAM Blocks: A Systematic Review and Meta-Analysis **Materials** 2023, 16. doi:10.3390/ma160829961 (**Q2**)

Calheiros-Lobo MJ, Carbas R, da Silva LFM, Pinho T. Impact of in vitro findings on clinical protocols for the adhesion of CAD-CAM blocks: A systematic integrative review and meta-analysis. **J Prosthet Dent** 2022. doi:10.1016/j.prosdent.2022.08.024 (**Q1**)

Calheiros-Lobo MJ, Costa F, Pinho T. Infraocclusion level and root resorption of the primary molar in second premolar agenesis: A retrospective cross-sectional study in the Portuguese population. **Dent Med Probl** 2022, 59, 195-207. doi:10.17219/dmp/146256 (**Q2**)

Calheiros-Lobo MJ, Calheiros-Lobo JM, Carbas R, da Silva LFM, Pinho T. Shear bond strength of CAD-CAM simulated single-retainer resin-bonded bridge for maxillary lateral incisor agenesis rehabilitation. **Eur J Dent** 2023 **(Q1)**

Submitted in the scope of this thesis

Calheiros-Lobo MJ, Carbas R, da Silva LFM, Pinho T. Effect of the Modulation of the Adhesive Interface between a CAD-CAM Hybrid Ceramic adherend and Three Luting Cements on Shear Bond Strength: In Vitro Study. **J Adhes Dent** 2023. (**Q1**) (submitted, under review)

CHAPTER 1

INTRODUCTION

1 Introduction

1.1 Setting of the problem and motivation

Complementary esthetic rehabilitation after orthodontic treatment in clinical situations of maxillary lateral incisor agenesis (MLIA) may be complex and far from consensual.[1,2] Treatment planning in an MLIA case must consider and evaluate the esthetic expectations and potential ongoing growth of the patient and well-coordinated interdisciplinary management.[2,3] MLIA has esthetic and functional impacts, thus smile analysis with different variables of esthetic perception, coupled with tridimensional data, and specific planning software are needed to achieve optimal results.[4,5] Treating skeletal malocclusion in teenagers is a difficult task due to changeable final facial growth, and the challenge becomes even greater in the presence of dental anomalies, which is the case of MLIA that frequently compromise normal function and esthetics.[3,6]

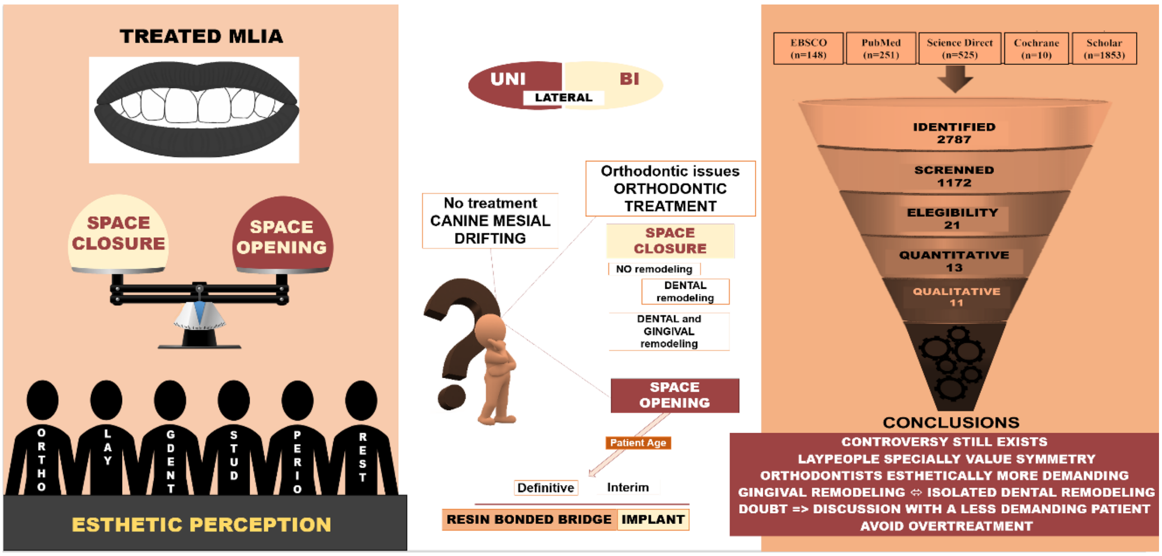


Figure 1 - Graphical representation of the treatment decision dilemma in clinical situations of MLIA[2]

MLIA is also frequently part of the incisor-premolar hypodontia,[7,8] and patients with agenesis of second premolars have a significantly higher prevalence of microdontia of maxillary lateral incisors.[9] In severe hypodontia cases, the most common patterns include the agenesis of the maxillary lateral incisor and both premolars,[8,10] making the treatment even more challenging. In both agenesis, the primary tooth can be retained, but unlike the mandibular primary second molar, which can be retained with good functional conditions for at least up to 25 years,[3] the primary lateral incisor is often lost within a few years due to resorption induced by intraosseous canine mesialization.[11,12]

Modern adhesive techniques with restorative materials,[13] usually done in cases with space closure, can be necessary at an early age, with necessary long-term adaptations.[5] If space opening is the option, a tooth implant or a resin-bonded bridge (RBBs),[1] can be an option. Dental implants require skeletal maturity, may be contra-indicated, the patient may not be able to afford it, or there is still no scientific evidence for the best therapy to follow,[2,14] what makes the RBBs an option and a minimally invasive approach.[15]

Traditionally placed with tooth preparation, RBBs can be placed with minimal or no tooth preparation, but loss of adhesion interface can occur.[16] Advances in adhesive dentistry and technology have expanded alternative RBBs preparation designs and materials.[15] Yttria partially stabilized zirconia (Y-TZP) has superior mechanical properties and superior resistance to fracture compared to conventional dental ceramics.[17] Despite investigations, the bonding mechanism between zirconia and the veneering ceramic is hazardous with chipping and debonding and remains poorly understood.[18] One solution is to not use veneered ceramics. A CAD-CAM ceramic adhered to a CAD-CAM zirconia framework without manual steps or full-contour zirconia RBBs has been proposed. However, antagonist enamel wear is a concern and more wear-friendly materials are required. Furthermore, Y-TZP suffers from low-temperature aging degradation, leading to in-mouth degradation.[17]

CAD-CAM materials are versatile and are emerging as the material of choice for many restorations. Still, proper clinical- and research-based evidence confirming their success and durability is needed before recommending them as the best for patient care.[19,20]

Adhesive restorations rely on bonding systems to form a micromechanical bond with the tooth,[21] although chemical interactions may occur between functional monomers and some tooth components with potential benefits.[22]

Enamel varies in thickness, has a high elastic modulus, a high compressive strength, and a low tensile strength, supports dentin to withstand masticatory forces,[23] and if treated with phosphoric acid, it can be infiltrated with a resin material to produce a micromechanical bond.[24]

Resin cements are widely used to adhere to non-metallic restorations,[23] so bond strength tests are essential tools to study their mechanical performance,[25] as mechanical, thermal, and passive hydrolysis may occur in the mouth with consequent loss of adhesive joint performance.[26]

The cement thickness and bonding conditions influence the performance of cemented ceramic restorations, as demonstrated by 2-dimensional finite elements analysis and physical tests, with the bonding effect disappearing under a large cement layer,[27] allowing us to believe that mechanical bonding may also play a significant role in the integration of anterior zirconia-based restorations, despite the controversial effect of surface treatments on the bonding strength of porcelain to zirconia.[17] The inherent non-polar nature of zirconia, which results in poor bonding ability to the tooth structure and/or overlaying ceramics, and its inert nature with resistance to chemicals that could improve the bond strength, and also to silane agents because of its absence in silica compounds, makes it a difficult material to bond in the mouth, causing anxiety to work with, despite its tempting high esthetic appearance.[28]

This motivated us to pursue more elastic and straightforward materials, such as dual-network structured ceramics or glass-ceramics enriched with zirconia. Moreover, despite the vast amount of adhesive cement and CAD-CAM materials available, the best match to achieve a lasting and efficient adhesive joint is yet to be found and is controversial.[20]

A suitable combination of a surface treatment and an adhesive cementation system requires a standardized protocol to allow a good bonding effect.[20] Further advances in adhesive clinical dentistry and alternative tooth preparation designs must be developed to accommodate the new minimally invasive restorative treatments.[15]

1.2 Objectives

1.2.1 General objectives

The main goal of the present study was to analyze the in vitro performance of monolithic ceramic materials that can be used as resin-bonded fixed dental bridges (RBBs) in patients with maxillary lateral incisor agenesis (MLIA) after space opening by orthodontic treatment.

1.2.2 Specific objectives

- Determination of shear bond strength of selected monolithic ceramics adhered with different cement types.
- Select the best adhesive strategy to lute the selected CAD-CAM monolithic ceramics with the selected adhesive cement.

- Comparison of the effects of different cement luting types on the fracture resistance of resin-bonded bridges.
- Comparison of fracture resistance between new monolithic ceramics and yttria-stabilized zirconia (Y-TZP).
- Determination of fracture resistance of new monolithic ceramics compared to yttria-stabilized zirconia (Y-TZP) when cemented to natural teeth.
- Identify a candidate artificial material to substitute natural incisor teeth in shear bond tests.

1.3 Research methodology

This work was developed to identify a CAD-CAM monolithic ceramic with good mechanical properties and a straightforward adhesive protocol for the rehabilitation of MLIA cases treated with orthodontic space opening. CAD-CAM monolithic ceramics with different compositions, combined with adhesive cement using different adhesive strategies, were assessed. In parallel, a CAD-CAM hybrid ceramic was also tested as a potential support substrate for future standardized shear bond tests, as it theoretically has mechanical properties similar to those of human teeth. The work was organized by task, and the scheme of the work is presented in Figure 2.

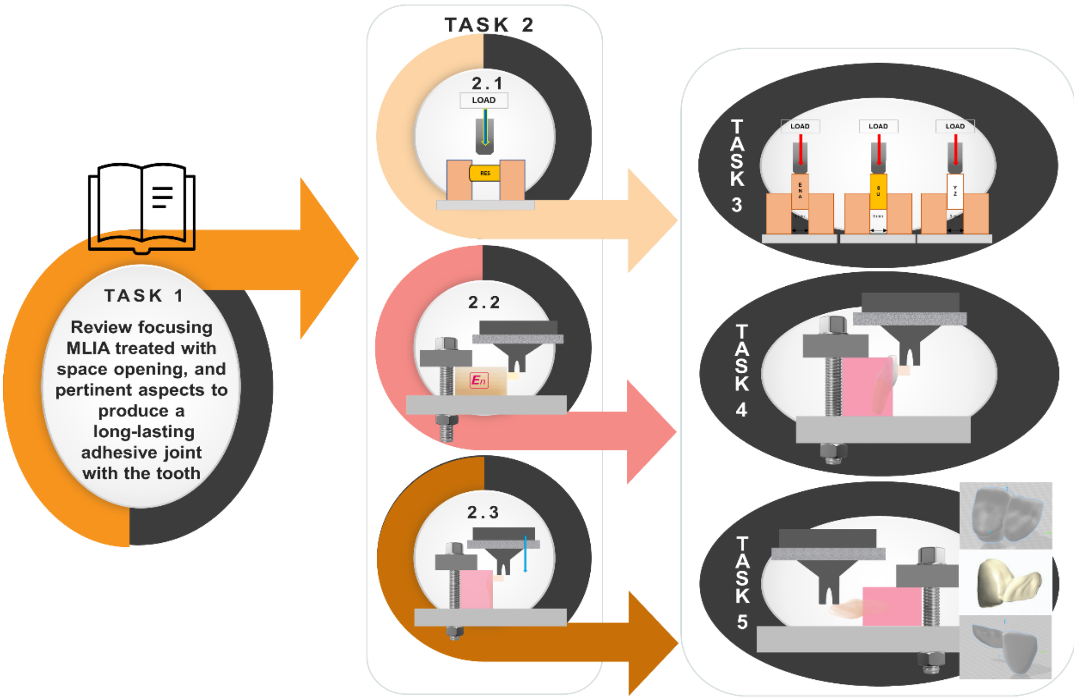


Figure 2 - Schematic representation of the workflow of the tasks performed in this work

Task 1: An integrative literature review focusing on pertinent aspects to produce a long-lasting adhesive joint to rehabilitate MLIA cases treated with space opening with CAD-CAM monolithic ceramics. This task searched for scientific evidence to theoretically support this research. All types of papers were considered because this research aimed at clinical application.

Task 2: Study of the adhesive joint.

Shear bond test (SBS), compression test, surface energy measurement, and mode of failure by digital optical microscopy were used. Several combinations of CAD-CAM monolithic ceramics adhered to different cements and substrates were assessed.

Task 2.1 – Specimen model factoring and preliminary tests. An innovative specimen model was searched to find a specimen capable of simulating the adhesive joint present in the MLIA cases. Three models were developed for this study.

Task 2.2 – Modulation of the adhesive interface. Several combinations of surface treatments and coupling agents used to produce adhesive joints between a CAD-CAM polymer-infiltrated ceramic network block and adhesive cements were assessed.

Task 2.3 – Search for an industrial alternative to human teeth. An artificial substrate (Frasaco® tooth) was tested as a base substrate for the assessment of adhesive cement shear strength, surface energy measurement, and mode of failure by digital optical microscopy.

Task 3: Testing a new RBB specimen model.

Data collected in Task 2 allowed us to test a new model fabricated with dimensions more similar to the mesiodistal space left by an absent maxillary lateral incisor. The model was equated to reduce bending during the tests, and three CAD-CAM monolithic ceramics adhered to the best-performing adhesive cement were tested in Task 2.

Task 4: Human teeth shear bond strength assessment.

As an alternative industrial material intended to replace human teeth as a substrate, it is essential to have shear bond strength test values for human teeth as a reference.

Task 5: Testing the simulated RBB for MLIA rehabilitation.

RBBs produced with four different CAD-CAM materials (three fabricated by drilling and one by 3D additive technology) were assessed by shear bond tests using the best-performing adhesive cement identified in Task 2.

1.4 Outline of the thesis

This thesis is supported by seven papers, six of which have already been published, and one submitted for publication.

Chapter 1 contains a brief description of the problem addressed, the motivation for this work, and its objectives. A summary of the experimental tasks and each paper is also provided. **Chapter 2** (Task 1) presents a literature review focused on the CAD-CAM ceramic candidates to rehabilitate MLIA cases, as well as the mechanisms, substrates, and modulation agents that intervene in the adhesive joint. **Chapter 3** (Tasks 2–5) clarifies the experimental procedures used throughout this work to assess the different combinations of components of this specific adhesive joint, as well as the strategy to identify a candidate material for future dental shear strength tests. **Chapter 4** presents some global considerations and main conclusions about the research topics, and **Chapter 5** presents suggestions for future work on these topics. The Appendices comprehend the publications developed within the scope of this thesis, which represent the research developed in detail, and supplementary information.

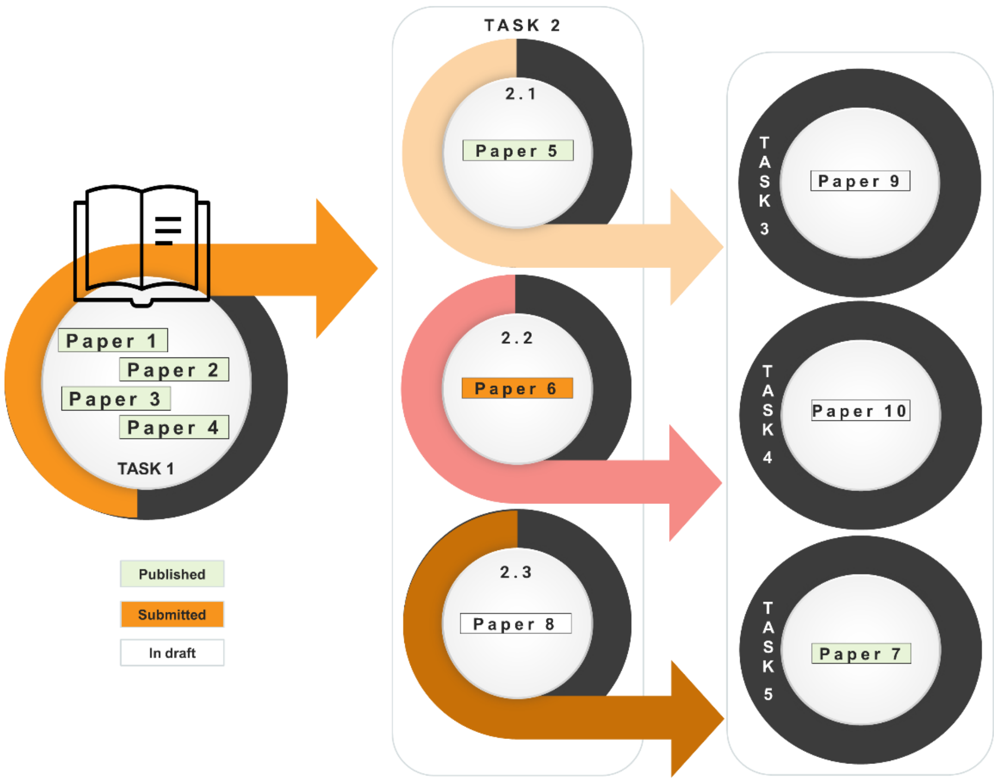


Figure 3 - Correspondence between tasks proposed and papers produced

1.5 Abstracts of the publications

Paper 1

Calheiros-Lobo MJ, Costa F, Pinho T. Infraocclusion level and root resorption of the primary molar in second premolar agenesis: A retrospective cross-sectional study in the Portuguese population. **Dent Med Probl** 2022, 59, 195-207, DOI:10.17219/dmp/146256 **(Q2)**

Abstract of Paper 1: An initial extensive review of the literature focused on dental agenesis, including MLIA, assessed the etiology, epidemiology, diagnosis, treatment options, prognosis, and functional aspects of this condition. A study evaluated the lifespan of the primary molar as a substitute, with root quality and occlusal adaptation, in cases of agenesis of M2P in a low-income population to determine whether the attitude of just vigilance could be the best clinical option when other clinical problems are absent. The agenesis of the second premolar (M2P) mandibular results in the retention of the second primary molar (2pm), infraocclusion, a reduced alveolar height and width, supra-eruption of antagonists, or movement of adjacent teeth. Infraocclusion affects the survival of the retained 2pm to a greater extent than root resorption. A total of 12,949 orthopantomograms were analyzed. Sixty-one patients (25 males and 36 females aged 7–36 years) were divided into group 1 (first permanent molar in occlusion) and group 2 (second permanent molar in occlusion). Vertical positioning to the occlusal plane, root condition, and the movement of the adjacent teeth were evaluated. Although the study has a cross-sectional design, root resorption, infraocclusion, the distance between the first permanent molar and the first primary molar or the first permanent premolar, and the width of the 2pm were correlated with age. The 2pm root resorption increased with age, which was more pronounced when the second permanent molar was also in occlusion. The mesial movement of the adjacent teeth was absent in all groups. 2 pm was often occluded, but the infra-occlusion increased with age. Age periods of 11–15 years and 21–25 years were critical for primary tooth loss. The second primary molar remains functional in the mandibular arch for up to 25 years. A well-documented no-intervention attitude based on clinical and radiographic data must be weighed in cases without orthodontic issues or with financial constraints.

Keywords: root resorption, infraocclusion, second primary molar, second premolar agenesis, mesial movement

Paper 2

Calheiros-Lobo MJ, Calheiros-Lobo M, Pinho, T. Esthetic perception of different clinical situations of maxillary lateral incisor agenesis according to populations with dental and non-dental backgrounds: A systematic review and meta-analysis. **Dent J** 2023, 11, 105, DOI:10.3390/dj11040105 **(Q2)**

Abstract of Paper 2: Treatment of unilateral or bilateral maxillary lateral incisor agenesis is challenging, time-consuming, expensive, and requires careful treatment planning, predictability, and esthetics. This review aimed to identify differences in esthetic perception between orthodontists, general dentists, differentiated dentists, and laypeople, which may interfere with treatment options. EBSCO, PubMed, ScienceDirect, Cochrane Library databases, and Google Scholar were searched using keyword pairing and a Boolean expression, "(congenitally missing OR agenesis OR hypodontia) AND (maxillary lateral incisors) AND (esthetic perception OR smile) AND (laypersons OR dental professional OR general dentist OR orthodontists)." Reviews and case studies were excluded. A total of 13 studies were selected for qualitative analysis (adapted ROBINS-I) and 11 were selected for meta-analysis ($p < 0.05$) after being subgrouped into the groups 'Opening vs. Closure' and 'No remodeling vs. Dental remodeling vs. Dental and gingival remodeling'. A meta-analysis evaluated the magnitude of the difference between groups based on differences in means and effect sizes ($\alpha = 0.05$; 95% CI; Z-value 1.96), revealing that the esthetic perception of maxillary lateral incisor agenesis treatment remains controversial even among professionals. Gingival remodeling was not valued compared to isolated dental remodeling. Studies lack rigorously comparable methodologies. Discussion with the patient is pertinent in doubtful situations, as the best treatment option remains unclear, and overtreatment should be avoided.

Keywords: maxillary lateral incisor agenesis; esthetic perception; laypersons; general dentist; dental professional; orthodontist

Paper 3

Calheiros-Lobo MJ, Carbas R, da Silva LFM, Pinho T. Impact of in vitro findings on clinical protocols for the adhesion of CAD-CAM blocks: A systematic integrative review and meta-analysis. **J Prosthet Dent** 2022, S0022-3913(22)00551-01. DOI:10.1016j.prosdent.2022.08.024 **(Q1)**

Abstract of Paper 3: Computer-aided design and computer-aided manufacturing (CAD-CAM) blocks have evolved rapidly, making it difficult to establish the best clinical protocol for bonding a given block and whether an established protocol is appropriate for a newly introduced product. This integrative systematic review and meta-analysis aimed to clarify whether the clinician can select the most efficient adhesion protocols for CAD-CAM blocks by reading published in vitro studies and implementing them in daily practice. Based on the population, intervention, comparison, and outcome (PICO) strategy, 3 databases were searched for in vitro studies, randomized clinical trials, prospective or retrospective studies, and case reports from January 1, 2015, to July 31, 2021. A meta-analysis analyzed 28 studies to calculate the mean difference between the best and worst protocols for each author and block with a random-effects model (α=.05). From 508 relevant studies, 37 in vitro studies, 2 clinical studies, and 1 clinical report were selected for data extraction and qualitative analysis. Vita Enamic, IPS e.max CAD, LAVA Ultimate, and Vita Mark II blocks were the most studied, and RelyX Ultimate was the most used luting cement. The meta-analysis confirmed the null hypothesis that the evidence-based efficacy of clinical protocols to bond CAD-CAM blocks remains controversial ($P<.05$). There are objective standards for individual in vitro tests, but studies lack standardization. Some tested protocols were more efficient than others. Randomized clinical trials and well-documented clinical situations were almost nonexistent, making the direct application of in vitro findings in clinical practice impossible.

Keywords: CAD-CAM, ceramics, blocks, adhesion, bonding, protocol, cement.

Paper 4

Calheiros-Lobo MJ, Vieira T, Carbas R, da Silva LFM, Pinho T. Effectiveness of self-adhesive resin luting cement in CAD-CAM Blocks: A systematic review and meta-analysis. **Materials** 2023, 16, DOI:10.3390/ma160829961 **(Q2)**

Abstract of Paper 4: Self-adhesive resin cements (SARCs) are used because of their mechanical properties, ease of use of cementation protocols, and lack of requirements for acid conditioning or adhesive systems. SARCs are generally dual-cured, photoactivated, and self-cured with a slight increase in acidic pH, allowing for self-adhesiveness and increasing resistance to hydrolysis. This systematic review assessed the adhesive strength of SARC systems luted to different substrates and computer-aided design and manufacturing (CAD/CAM) ceramic blocks. The PubMed/MedLine and Science Direct databases were searched using the Boolean formula [((dental or tooth) AND (self-adhesive) AND (luting or cement) AND CAD-CAM) NOT (endodontics or implants)]. Of the 199 articles obtained, 31 were selected for the quality assessment. Lava Ultimate (resin matrix filled with nanoceramic) and Vita Enamic (polymer infiltrated ceramic) blocks were the most tested. Rely X Unicem 2 was the resin cement most tested, followed by Rely X Unicem > Ultimate > U200, and μTBS was the most widely used test. The meta-analysis confirmed the substrate-dependent adhesive strength of SARCs, with significant differences between them and between SARCs and conventional resin-based adhesive cement ($\alpha < 0.05$). SARCs are promising. However, one must be aware of the differences in the adhesive strengths. An appropriate combination of materials must be considered to improve the durability and stability of restorations.

Keywords: dental, tooth, self-adhesive, luting, cement, CAD-CAM, monolithic ceramics, blocks

Paper 5

Calheiros-Lobo MJ, Calheiros-Lobo JM, Carbas R, da Silva LFM, Pinho T A Polymer-Infiltrated Ceramic as Base Adherent in an Experimental Specimen Model to Test the Shear Bond Strength of CAD-CAM Monolithic Ceramics Used in Resin-Bonded Dental Bridges. **Coatings** 2023, 13, 1218. https:// doi.org/10.3390/coatings13071218 **(Q2)**

Abstract of Paper 5: Experimental fabrication, similar to prosthetic laboratory and clinical procedures, best predicts future clinical performance. A hybrid ceramic adherend, mechanically similar to a human tooth, was tested by comparing the shear bond strength (SBS) and fracture mode of four restorative materials adhered with a dual-cure adhesive cement. Surface energy, shear bond strength (SBS), and fracture mode were assessed. Vita Enamic (ENA), Vita Suprinity (SUP), Vita Y-TPZ (Y-ZT), and a nanohybrid composite (RES) (control group) cylinders, adhered with RelyX Ultimate to ENA blocks were assembled in experimental specimens simulating a 3-unit resin-bonded dental bridge. The ENA adherend was ground or treated with 5% hydrofluoric acid for 60 seconds. Monobond Plus was used as the coupling agent. Mean shear stress (MPa) was calculated for each group. Forest plots by material elaborated after calculating the difference in means and effect size (α= 0.05; 95% CI; Z-value = 1.96) revealed significant differences in the shear force behavior between materials ($p < 0.01$). RES (69.10 ± 24.58 MPa) > ENA (18.38 ± 8.51 MPa) > SUP (11.44 ± 4.04 MPa) > Y-ZT (18.48 ± 12.12 MPa). Y-ZT and SUP exhibited pre-test failures. SBS was not related to surface energy. The failure mode in the Y-ZT group was material-dependent and exclusively adhesive. ENA is a potential adherend for dental materials SBS tests. In this experimental design, it withstood 103 MPa of adhesive stress before cohesive failure.

Keywords: adhesive stress; bonding; hybrid ceramic; CAD-CAM; resin cement; resin-bonded bridge; shear bond strength; surface energy; surface treatment; zirconia-reinforced lithium disilicate; yttria-stabilized tetragonal zirconia

Paper 6

Calheiros-Lobo MJ, Carbas R, da Silva LFM, Pinho T. Effect of the Modulation of the Adhesive Interface between a CAD-CAM Hybrid Ceramic adherend and Three Luting Cements on Shear Bond Strength: In Vitro Study. **J Adhes Dent** 2023. **(Q1)**

(Submitted, under review)

Abstract of Paper 6: To evaluate a CAD-CAM hybrid ceramic as a potential adherend for shear bond tests by surface modulation and adhesion with three types of luting cement.

Panavia SA (SA), RelyX Ultimate (RU), and Vita Adiva IA-Cem (IA) cylinders adhered to VITA Enamic blocks were used. Block surface treatment was cutting or 5% hydrofluoric acid for 60s. VITA Adiva C-Prime (CP) and Monobond Plus (MB) were alternative coupling agents. Surface energy assessment (block and cement), shear bond strength (SBS), ultimate tensile strength, and fracture analyses were conducted. SA in the self-adhesive mode adhered to the only cut block was the control group (SA/0). Boxplots for SBS and forest plots by protocol were elaborated after calculating the difference in means and effect size (α=.05; 95% CI; Z-value=2.83). The RU/MB group had the best SBS score ($p < 0.001$). RU (38.45 ± 2.97 MPa) and IA (17.35 ± 2.39 MPa) performed better with MB and SA (24.35 ± 3.30 MPa) with CP. CP (24.35 ± 3.30 MPa) > MB (19.89 ± 2.23 MPa) increased the SBS of SA compared to the self-adhesive mode (SA/0, 13.21 ± 4.74 MPa). RU/CP showed inconsistent SBS. The surface energy of the substrates had no direct influence on the SBS. The polymerization efficacy of IA-Cem raised doubts. RU fluorescence was helpful for excess removal. Except for SA/0, the tested combinations attain ed SBS values within those aimed for adhesion to tooth substrates. The coupling agent and cement affected the SBS under the test conditions. RU performed significantly better ($p < 0.001$) than the other cements with both coupling agents. MB performed better as a coupling agent, except for SA. The Enamic block is a potential adherend for SBS tests.

Keywords: bonding, Enamic, hybrid ceramic, luting cement, shear bond strength, surface energy, surface treatment

Paper 7

Calheiros-Lobo MJ, Lobo J, Carbas R, da Silva LFM, Pinho T. Shear bond strength of CAD-CAM simulated single-retainer resin-bonded bridge for maxillary lateral incisor agenesis rehabilitation. **Eur J Dent** 2023 **(Q1)**

Abstract of Paper 7: Maxillary lateral incisor agenesis, treated orthodontically by opening the space, requires complimentary esthetic rehabilitation. Interim resin-bonded bridges (RBB) until skeletal maturity is achieved to place an implant-supported crown, or as definitive rehabilitation in case of financial restrictions or implant contraindications, can be equated. Scientific evidence for the best material still needs to be confirmed. Computer-aided design and computer-aided manufacturing (CAD-CAM) materials are promising versatile restorative options. Partially yttria-stabilized is an interesting, tough esthetic material. However, despite research, its micromechanical bonds and chemical interactions with substrates remain hazardous. To find a straightforward material to deliver resin-bonded bridges for non-prep tooth replacement in MLIA, definitive or interim. Single-retainer RBB made from CAD-CAM ceramic blocks (Vita Enamic (ENA), Suprinity (SUP), and Y-ZPT) and a 3D printed material (ABS) were evaluated by shear bond strength (SBS) and mode of failure, after adhesion with Rely X Ultimate used in a 3-step adhesive strategy. The mean ± standard deviation SBS values were ENA (24.24 ± 9.05 MPa) < ABS (24.01 ± 1.94 MPa) < SUP (29.17 ± 4.78 MPa) < Y-ZPT (37.43 ± 12.20 MPa). The failure modes were adhesive for Y-ZPT, cohesive for SUP and ENA, and cohesive with plastic deformation for ABS. **Conclusions**: Vita Enamic, Suprinity, Y-ZPT zirconia or 3D printed ABS RBBs are options to rehabilitate MLIA situations. The option for each material is conditioned to an estimation of the time of use and the necessity of removal for orthodontic or surgical techniques.

Keywords: adhesion, monolithic ceramics, shear bond strength, surface energy, CAD-CAM, 3D additive manufacturing

CHAPTER 2
LITERATURE REVIEW

2 LITERATURE REVIEW (TASK 1)

In this chapter, the main aspects of the adhesion of CAD-CAM ceramics to the tooth structure and the effects of combining materials that intervene in the adhesive joint aimed at adhering CAD-CAM ceramics to the tooth with a long-lasting performance are addressed.

Additional information and details can be found in the appended review papers. Papers 1 and 2 focused on the etiology, epidemiology, diagnosis, treatment plan, prognosis, and functional and esthetic aspects of MLIA condition, and Papers 3 and 4 focused on CAD-CAD ceramics, adhesion protocols, and adhesive-luting cements.

2.1 General aspects

CAD-CAM technology (Computer-Aided Design/Computer-Aided Manufacturing technology), introduced for the aerospace industry, became available for the dental clinical practice in the late 80s and revolutionized the field of dentistry with significant developments in the last 30 years, regarding the reading of dental preparations, virtual design programs, available materials and mode of restoration production, with an increasingly comprehensive demand for the treatment of patients with fixed restorations.[19,29-31]

The clinical performance of contemporary dental ceramics is based on various factors, ranging from the intrinsic physical properties of the materials to the fabrication process. Clinical protocols and the oral environment can also deteriorate fragile materials.[32]

Monolithic ceramics associated with CAD-CAM technology appeared in an attempt to skip the technical and mechanical issues of layered fixed prosthesis, and so far, with high survival and low complication rates, but randomized controlled trials (RCTs) are needed to reassess these clinical performances, mainly comparing them with the performance of veneered restorations.[33] The number of RCTs testing complete digital workflows in fixed prosthodontics is still low, and scientifically proven recommendations for routine clinical practice cannot be provided.[20,34] Research based on high-quality clinical trials is slower than the industrial progress of available materials for digital workflow.[20] Future research with well-designed RCTs, including follow-up observation, is compellingly necessary for the field of complete digital processing.[34]

In 1999, Kelly[35] advocated that traditional fracture tests of single-unit all-ceramic prostheses are inappropriate because they do not create the failure mechanisms observed in retrieved clinical specimens since significant differences occur between the failure behavior created during traditional load-to-failure tests and that during the clinical failure of all-ceramic restorations.

Current evidence suggests that the best predictors of future clinical performance are tests performed using: (1) restoration design that represents the anticipated clinical design as closely as possible (e.g., full anatomy, variations in the length of the interproximal wall, core shape, and thickness, veneer thickness); (2) fabrication procedures that closely anticipate laboratory and clinical procedures (e.g., sandblasting before cementation with typically used protocols, pressed vs. layered veneers, etc.); (3) supporting structures that will be used clinically (e.g., implant- vs. dentin-supported); and (4) fatigue loading in water with sliding contacts.[36]

Modified in vitro experimental research designs, such as ours, that try to simulate clinical conditions, may help to understand the long-term behavior of the materials and prosthesis, and are supported by the evidence that so far few experimental protocols can be transposed directly from the laboratory to the clinic context.[20]

The high innovation rate in CAD-CAM materials and technology demands good knowledge from practitioners for the optimal and successful use of all available options,[37] Therefore, testing adhesive protocols brought from the clinic to the laboratory and not the other way around may contribute to clarifying the effectiveness of adhesive procedures during a regular consultation as part of the rehabilitative treatment for MLIA.

In a recent survey[38] conducted in Germany with data collected from 688 participants, most dentists selected appropriate restorative materials according to the individual clinical settings presented in the survey. For the fixed 3-unit anterior partial prosthesis, the time since graduation was associated with the preference for a specific restorative material. In addition, some dentists have selected lithium disilicate ceramics for situations beyond their recommended indication range, which may reflect a mistake or the need for more information. Ceramic was the most preferred material to fabricate a 3-unit fixed partial prosthesis independent of the location of the abutment teeth, with veneered zirconia as the favored option.[39]

CAD-CAM technology can help clinicians provide high-strength and esthetic restorations, as accurate impression techniques, precise fabrication, and laboratory finishing procedures would reduce the effort of chairside alterations, thus decreasing the complications associated with fractured restorations. Moreover, high-translucency monolithic zirconia was recently developed, to be used in anterior restorations without fearing the opacity of conventional zirconia.[40]

2.2 Monolithic ceramics

Most commercially available CAD-CAM esthetic materials fall into four classes: glass-matrix ceramics, polycrystalline ceramics, indirect composites, and hybrid ceramic.[41,42]

Currently, polycrystalline ceramic zirconia is considered the best material in terms of mechanical behavior. However, chipping or lamination of the veneer material was recorded as one of the most common complications of zirconia restorations, along with some issues related to bonding protocols.[42,43] Y-TZP (yttria-stabilized tetragonal zirconia polycrystal) is widely used but lacks the esthetics of glass ceramics and has been somewhat restricted to the posterior region.[44]

Restoration designs driven by patient clinical problems, tooth preparation, type of cementation, material thickness, and mechanical properties are the main factors affecting the fracture resistance of all-ceramic restorations. To overcome this problem and attempt to deal with more user-friendly protocols, manufacturers have tried to develop new materials by incorporating strong inorganic particles, such as zirconia particles or a polymer-infiltrated ceramic network (PICN).[45] VITA Suprinity® (VITA-Zahnfabrik, Bad Säckingen, Germany) and VITA Enamic® (Vita Zahnfabrik, Bad Säckingen, Germany) are examples of such materials.

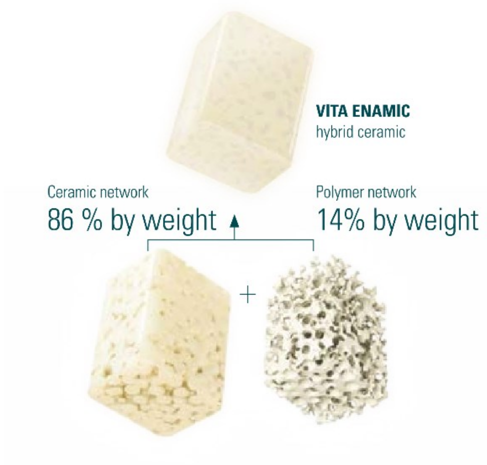
In an “in silico” simulation on stress distribution in occlusal veneers, a direct correlation between restoration thickness and concentration of tensile stresses was detected, in the following decreasing order for the simulated materials: HT-Z (high translucency zirconia) (highest stress concentration), LS_2 (lithium disilicate), FC (feldspathic ceramic), ZLS (zirconia reinforced lithium disilicate), and PICN. Furthermore, the type of restorative material influenced the stress concentration in the cement layer in the following decreasing order: PICN > HT-Z > ZLS > LS_2 > FC.[46]

Among the monolithic ceramics available, three, in particular, have characteristics that make them interesting for the rehabilitation of MLIA in the form of resin-bonded bridges.

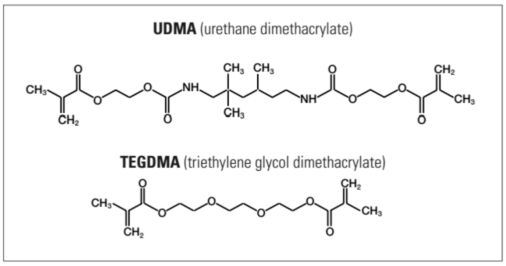
2.2.1 VITA Enamic®

Figure 4 - VITA Enamic® CAD-CAM block

VITA Enamic® (ENA) (Fig. 4) is a polymer-based hybrid ceramic (PICN) with a high flexural strength and a low flexural modulus compared to conventional ceramic materials. It shows mechanical properties between porcelains and resin-based composites, reflecting its microstructural components (Fig. 5).[47]



Composition of the polymer network (14 wt% / 25 vol%)



Composition of the ceramic network (86 wt% / 75 vol%)

Silicon dioxide	SiO_2	58 – 63 %
Aluminum oxide	Al_2O_3	20 – 23 %
Sodium oxide	Na_2O	9 – 11 %
Potassium oxide	K_2O	4 – 6 %
Boron trioxide	B_2O_3	0,5 – 2 %
Zirconia	ZrO_2	< 1 %
Calcium oxide	CaO	< 1 %

	VITA ENAMIC	Standard value
Static fracture load [N] (SD)	2,766 (98)	None specified
Density [g/cm³]	2.1	None specified
Flexural strength [MPa]	150 – 160	ISO 10477: ≥ 50 ISO 6872: ≥ 100
Modulus of elasticity [GPa] (SD)	30 (2)	None specified
Abrasion [µm]	In the same range as Mark II, veneering ceramics	None specified
Extension in the case of fracture [%] (SD)	0.5 (0.05)	None specified
Weibull modulus	20	None specified
Hardness [GPa]	2.5	None specified
Fracture toughness [MPa√m]	1.5	None specified
Adhesion with veneering material [MPa]	Without silane: 12 With silane: 27	ISO 10477: ≥ 5
Shear strength, cementation [MPa]	RelyX Unicem: 21, Variolink II: approx. 27, RelyX Ultimate approx. 31	None specified

Figure 5 - Chemical, technical, and physical data of Vita Enamic® according to the manufacturer[48]

The combination of low flexural modulus and high flexural strength of this material creates expectations of increased ability to withstand loading by undergoing more elastic deformation before failure, favoring mechanical compatibility with enamel and dentin and therefore more similar to human tooth behavior.[49]

ENA has flexural properties close to those of human dentin; therefore, it is an acceptable choice for single-unit restorations in this specific aspect. In contrast, it has low stiffness properties, which is a concern.[50] It is also known for its ability to bond to the tooth structure, which helps to create a strong and durable restoration.

On the other hand, extreme conditions, such as prolonged water storage, autoclave treatment, and thermal cycling, significantly decrease its flexural strength, while exposure to hydrochloric acid or cyclic loading did not affect the properties, despite some loss of surface material.[51]

The typical double network microstructure of the ENA results in a honeycomb polymer-based structure important for micromechanical bonding and adhesive interface performance,[52] allowing for decreased crack propagation.[53]

Given the susceptibility of polymeric materials to bacterial activity, the resistance to biodegradation of this hybrid ceramic may create some concerns that should not be present in an all-ceramic system.[52]

2.2.2 VITA Suprinity PC®

Figure 6 - VITA Suprinity® CAD-CAM block[54]

VITA Suprinity PC® (SU) (Fig. 6) with only a few years on the market is a new generation of glass ceramic material enriched with ± 10 wt% zirconia and 0.1 by weight lanthanum oxide, resulting in a pre-crystallized zirconia-reinforced lithium silicate ceramic (ZLS). It is fine-grained (0.5-0.7 µm) and homogeneous in structure, which guarantees excellent material quality, consistently high load capacity and long-term reliability, and easy milling and polishing (Table 1). His high translucency, fluorescence, and opalescence allow esthetic results and broad indications that include anterior and posterior crowns, suprastructures on implant abutments, veneers, inlays, and onlays.[54]

Concerning the biocompatibility and mechanical properties of ZLS, data are still scarce, often controversial, and limited to short-term observational periods. It is a promising ceramic that requires further in vitro/in vivo studies to accurately define mechanical and biological properties, mainly in the long-term performance of restorations produced with such material.[55]

Table 1 - Chemical, technical, and physical data of Vita Suprinity® provided by the manufacturer[54]

Components	Wt%
SiO_2	56 – 64
Li_2O	15 – 21
K_2O	1 – 4
P_2O_5	3 – 8
Al_2O_3	1 – 4
ZrO_2	8 – 12
CeO_2	0 – 4
La_2O_3	0.1
Pigments	0 – 6

Test	VITA SUPRINITY	Standard ISO 6872
3-point flexural strength	approx. 420 MPa*1	> 100 MPa
3-point flexural strength, precrystallized	approx. 180 MPa	None specified
Biaxial strength	approx. 540 MPa*2	> 100 MPa
Modulus of elasticity	approx. 70 GPa	None specified
Weibull modulus	approx. 8.9	None specified
Fracture toughness (SEVNB)	approx. 2.0 MPa $m^{0.5}$	None specified
Hardness	approx. 7000 MPa	None specified
CTE	approx. 11.9–12.3 · 10^{-6}/K	None specified
Transformation temperature (TG)	approx. 620 °C	None specified
Softening temperature	approx. 800 °C	None specified
Chemical solubility	approx. 40 µg/cm²	< 100 µg/cm²

2.2.3 VITA Y-TPZ®

Zirconium oxide (ZrO_2) was used in 1969 for medical purposes as a novel hip head replacement instead of titanium or alumina prostheses.[43] In dentistry, the partially stabilized zirconia (PSZ) class, known as first-generation zirconia, is stabilized with yttrium oxide and a mixture of monoclinic, tetragonal, and cubic crystals, but is currently discontinued.

Vita YZ HT (YZ) (Fig. 8) is a conventional zirconia stabilized by 3 mol% yttria (3Y-TZP) with 85–90% of the tetragonal phase (TP), which has been used in the last 15 years.

Figure 7 – Example of one of the VITA Y-TPZ® CAD-CAM blocks [56]

YZ has a high flexural strength (1200–1500 MPa) and an opaque white appearance as the main characteristics (Table 2). For the most part, this variant is composed of tetragonal crystals of a few hundred nanometers, but to keep the material stable at room temperature, approximately 3 mol% of yttrium oxide is added to the composition, which is why it is sometimes called 3Y zirconia.[57] Due to opacity, manual or industrial dyeing coupled with a veneering technique is mandatory for esthetic issues. Their physical and mechanical characteristics are references for new generations. The recent translucent zirconia (third generation 5Y-TPZ contains more yttria (≥ 5 mol%), reduced grain size, and around 50% of the final cubic phase.[57] This crystallographic isotropic cubic phase decreases light scattering at the grain boundaries, making the material more translucent.[44,58]

Table 2 - Chemical, technical, and physical data of VITA YZ HT® provided by the manufacturer[56]

Components [Wt%]	**VITA YZ** T	**VITA YZ** HT	**VITA YZ** ST	**VITA YZ** XT
ZrO_2	90 – 95	90 – 95	88 – 93	86 – 91
Y_2O_3	4 – 6	4 – 6	6 – 8	8 – 10
HfO_2	1 – 3	1 – 3	1 – 3	1 – 3
Al_2O_3	0 – 1	0 – 1	0 – 1	0 – 1
Pigments	0 – 1	0 – 1	0 – 1	0 – 1
Components [unit]	**VITA YZ** T	**VITA YZ** HT	**VITA YZ** ST	**VITA YZ** XT
CTE 1) [10^{-6}/K]	10.5	10.5	10.3	10.0
Chemical solubility 1) [µg/cm²]	< 20	< 20	< 20	< 20
Sintering density 2) [g/cm³]	6.05	6.08	6.05	6.03
3-point flexural strength 1) [MPa]	1200	1200	> 850	> 600
Fracture toughness 3) (CNB method) [MPa $m^{0.5}$]	4.5	4.5	3.5	2.5
Modulus of elasticity 4) [GPa]	210	210	210	210
Hardness 5) [HV 10]	12	12	13	13
Weibull modulus 1)	14	14	13	11

1) Determination according to DIN EN ISO 6872:2015
2) Determination according to DIN EN 623-2:1993
3) Determination according to ISO 24370:2005
4) Determination according to DIN EN 843-2:2007
5) Determination according to DIN EN 843-4:2005

These alterations reduce the strength of the material, as the cubic phase does not undergo stress-induced transformation, but still exhibits superior mechanical behavior compared to lithium disilicate glass-ceramic,[59] and reduced opacity compared to 3Y-TZP, making it more suitable and predictable for monolithic restorations (Fig. 10).[44,60]

Due to reduced stress-induced toughening because of reduced strength and toughness, the most translucent 5Y-TPZ materials are limited to single-unit crowns and short-span fixed dental prostheses (RBBs) in the anterior zone. In clinical situations requiring stronger restorations (multiunit posterior restoration or rehabilitation of bruxism patients), conventional 3Y-TZP materials can be used with strength advantages over lithium disilicate,[61,62] but with just a translucency of around 70%.[63] Still, monolithic zirconia types with a higher yttria content and a higher cubic/tetragonal ratio are inferior to the unique translucency of glass-ceramics and not comparable to enamel in translucency.[64]

5Y-TPZ does not have measurable material wear and opposing enamel wear similar to that of lithium disilicate glass-ceramic,[58,61] and close to the recognized gold standards, type III gold alloy, and natural enamel.[65,66] Compared to other ceramic materials, monolithic zirconia causes minimal wear of antagonists if properly polished, so this hard polycrystalline material can be used safely to replace natural enamel.[67]

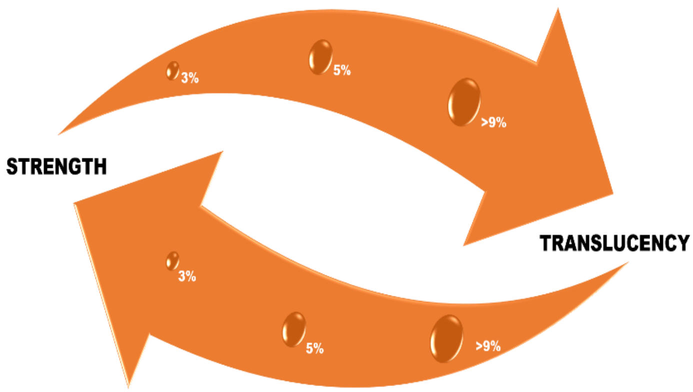


Figure 8 - Graphical representation of the variation of strength and translucency by yttria content in zirconia ceramics

Furthermore, several of the clinical properties of 5Y-TPZ must be evaluated to determine whether this material will perform similarly to previous iterations of dental zirconia in terms of bonding ability if conditioned by the use of airborne particles and primers or adhesives containing 10-methacryloxydecyl dihydrogen phosphate (MDP), as variations may occur.[20,68]

A higher yttria content, while improving zirconia esthetically, sacrifices mechanical performance, so a decrease in the thickness of ZrO_2 to less than 1.5 mm may be contraindicated, particularly in areas of high bearing stress, as it has lower mechanical properties than 3-mol% of Y-TZP, making it more susceptible to breakage.[60,64,69] Thickness, composition, microstructure, and cementing agent are crucial in the tetragonal phase of monolithic zirconia.[62,63]

Significant variations exist between studies in terms of methodology, sample size, and commercial products used so that no other safe conclusion can be drawn apart from promising results.[67] This conclusion agrees with recent systematic reviews that investigated the survival and complication rates of zirconia-ceramic and metal-ceramic single crowns,[70] the survival and complication rates of fixed dental prostheses of zirconia-ceramic and metal-ceramic multiple-unit fixed dental prostheses,[71] and the adhesive protocols themselves, this last with meta-analysis.[20]

Altering sintering parameters alters the grain size, wear behavior, and translucency of zirconia, and clinical studies that investigate the influence of changing sintering parameters or methods on the clinical performance of monolithic zirconia restorations are lacking.[72]

Different yttria contents and differences in the aging behavior of newer generations of zirconia recommend cautious clinicians in extrapolating results from research in longevity focusing on older material,[37] although the few existing RCT studies reveal promising results.[73]

The high translucency of new generations of zirconia may be contraindicated, particularly in the case of underlying colored tooth stumps, as it reduces the masking potential of the restoration.[63] Therefore, it is essential to select and use the correct material according to the range of indications,[74,75] and precise knowledge about the chemical modifications of zirconia in the new generations is still missing.[63]

2.3 Adhesive joints

Adhesion or cohesion includes an adherend, an adhesive, and an intervening interface. Bonding with adhesives involves attaching two or more dissimilar materials that do not have a natural affinity for each other without changing their characteristics. This runs with or without the help of a coupling material.[21,76]

Adhesion mechanisms can be classified into two main categories: mechanical and chemical. Mechanical adhesion or retention implies surface modification for surface roughness with the formation of macro- or microrugosities and relies on mechanical interlocking. Chemical adhesion involves modification of the surface chemistry, with chemical activation by a liquid with bonding affinity to both surfaces.[76-78]

2.3.1 Adhesive challenges

Retention of restorative materials, particularly RBBs, depends on the quality of the adhesive joint, which determines the quality of the bond at different interfaces. Not only is the interface between cement and dental tissue important, but the connection between cement and the surface of the restorative material also plays a crucial role.[79,80] The process involves adhesion and cohesion, [78,81] one between the substrates, and the other within each substrate (Fig. 9).

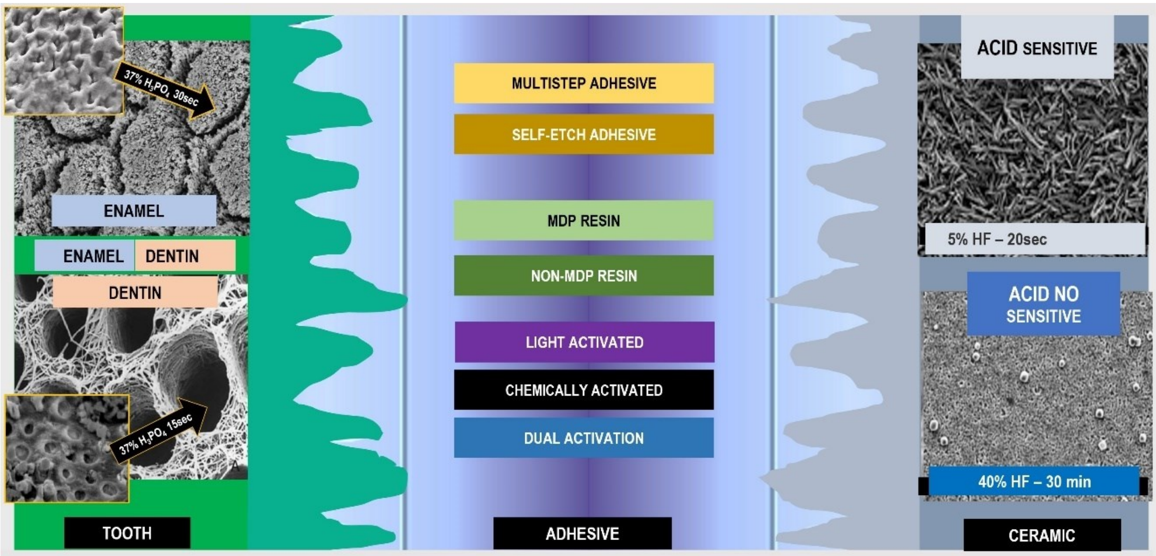


Figure 9 – Illustration of possible adhesive joints, different bonding strategies, and different materials between tooth substrates and ceramics

CAD-CAM restorative materials require a multistep bonding procedure, and the specific bonding strategy for each material is determined based on its composition.[20,41]

Today, it is expected that a resin cement should be biocompatible with enamel and dentin, should adhere effectively to most prosthodontic restorative materials, but also be resistant to functional, hydrothermal, and mechanical stress, and therefore resistant to failure.[82] It is accepted that adhesive luting reinforces the mechanical properties of CAD-CAM ceramics except for zirconia polycrystals, which is, by itself, a resistant material.[83]

2.3.2 Main factors influencing the bonding to ceramics

Surface energy and surface treatment

Surface energy is a term that defines the surface of a given substrate from high to low. It quantifies the disruption of intermolecular bonds that occurs when a surface is created, which is necessarily different in the bulk of the material. The adhesion is determined by the force of molecular attraction between different materials, and the strength of the attraction depends on the surface energy of the substrate. A high surface energy indicates a strong molecular attraction; therefore, it is easier to bond, whereas a low surface energy indicates weaker attractive forces, making it harder to bond (Figs. 10 and 11). Cutting a solid material into pieces disrupts its chemical bonds and increases its surface area, thus increasing its surface energy.[76,84]

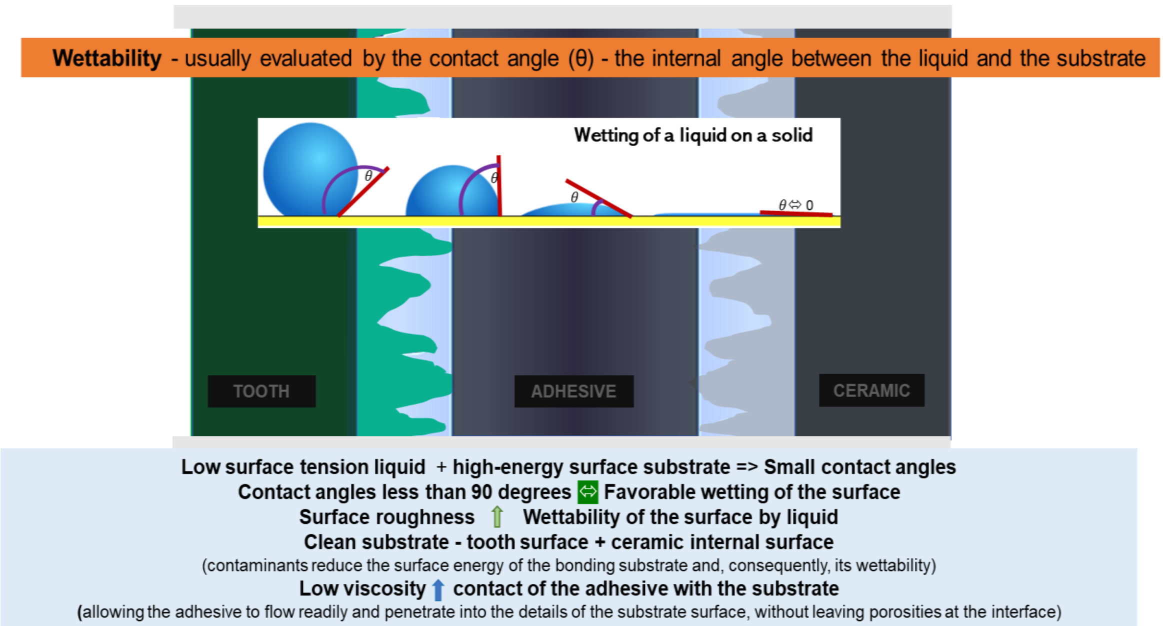


Figure 10 - Schematic representation of the contact angle and wettability results

Characterization of the interface before adhesion, during function, and after failure is helpful for investigations and remains a great challenge.[76] The surface treatment of each CAD-CAM material and the luting resin used influences the adhesion bond strength, so for each pair of materials, a specific adhesive cementation protocol must be used to obtain the highest bond strength.[20,85]

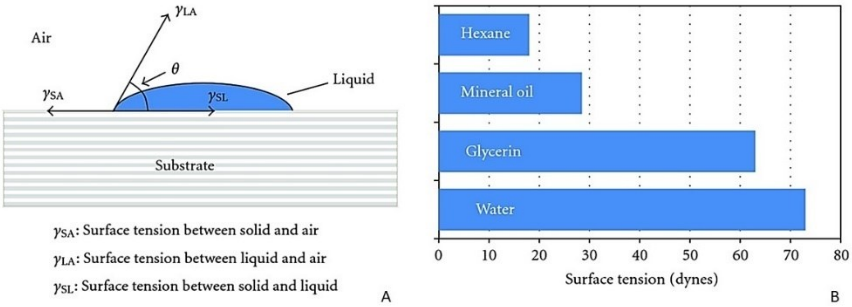


Figure 11 - Scheme of the interfacial tensions for a drop of liquid on a solid surface (A) and the surface tension of common liquids (B) (Adapted from von Fraunhofer – 2012).[81]

Chemical conditioning of the substrate surface (acid etching)

Mechanical interlocking is a mechanism by which an adhesive flows into morphological irregularities on the surface of a substrate before curing. It is commonly used to adhere dental materials and is considered the most effective means of creating solid joints.[76] To achieve this type of substrate, surface irregularities must be created on the surface.

Acid-sensitive CAD-CAM ceramics (for example, ENA and SU) undergo ceramic dissolution that increases with increasing concentration and duration of hydrofluoric acid (HF), both on the surface and in the depth of the material, with a higher strength bond to resin cement.[86,87]

Leucite-reinforced ceramics, hybrid ceramics, and lithium disilicate glass ceramics can be etched with 5-10% HF for 20-120 s without negative effects on the bond strength. Lithium disilicate can be etched from 30 s to 60 s with different concentrations of HF, but a 60 s etching time with 9.5% HF acid is suggested.[86-88]

The bond strength of a resin-luting cement to ceramics varies with pretreatment methods, with hydrofluoric acid followed by silanization being the common method with high values with feldspathic and lithium disilicate ceramics.[87,89]

It has been suggested that surface treatment with a self-etch ceramic primer promotes adhesion similar to that of HF when preparing the surface of lithium-disilicate ceramic, polymer-infiltrated ceramic, leucite-reinforced feldspathic ceramic, and lithium-disilicate glass ceramic for adhesion.[90] Furthermore, in these cases, the additional application of adhesive after surface treatments did not improve the bond strength,[90] allowing suppression of one clinical step. This opinion is still questioned, and some authors suggest that in vitro studies involving long-term clinically relevant artificial aging, and more clinical studies are required before this type of protocol can be considered an alternative to conventional surface treatment of glass-ceramic materials.[87,91] The etching efficacy of a self-etching ceramic primer is material dependent,[89] and is not dependent on the association with hydrofluoric acid or silane for chemical interaction or bonding stability.[92]

The crystalline nature of zirconia, with a dense crystal network and a small amount of glass matrix, makes it an acid-resistant material. Application of a 9.5% or 5% HF concentration induces no morphologic changes in its structure and does not increase surface roughness.[93] Even a 40% HF concentration, only produces nanoindentations that are probably insufficient to improve the strength of the adhesive joint.[93] For all this, combined mechanical and chemical treatment is essential to achieve efficient adhesion to zirconia.[94]

Mechanical conditioning of the substrate surface (sandblasting)

Airborne particle abrasion with aluminum oxide and tribochemical silica coating (Cojet® system, 3M ESPE, Minneapolis, MN, USA) is the pretreatment with more evidence in the literature to pretreat acid-resistant CAD-CAM blocks during physicochemical conditioning, modifying the block surface to increase adhesion.[94]

Airborne particle abrasion coupled with a zirconia primer is an accepted but not yet standardized protocol[20] that improves the shear strength of zirconia bonds to the enamel. It has been considered a clinically applicable surface treatment method to achieve resistance to degradation and durable bonding over time.[95,96]

In a research study,[97] it was found that specimens air-abraded with 50 μm Al_2O_3 powders exhibited higher μTBS values than those treated with 27 μm Al_2O_3 or 30 μm CoJet after silanization with MDP-silane and cemented with a dual-cure adhesive cement.

A meta-analysis[98] showed that Al_2O_3 particles between 30 μm and 110 μm and pressures between 0.20 and 0.40 MPa are commonly applied and that if used within these limits, airborne particle abrasion increases the flexural strength without causing damage to the material by introducing surface flaws.[99] Furthermore, 110 μm sand for 3Y-TZP, 90 μm sand for 4Y-TPZ and 25 μm sand for 5Y-TPZ has been suggested.[100]

Concerning air abrasion, the total time, distance, and angle of the procedure also matter, and 10 s/cm^2, 10 mm, and 90°, respectively, should be used.[100]

It is important to note that different chemical compositions of zirconia result in different topographic changes, with larger particles inducing more compressive residual stress related to the monoclinic tetragonal phase transformation for 3Y-TZP, while only 25 µm sized sand induces residual stress due to the low potential for cubic grain phase transformation in 5Y-TPZ,[98,101] that is, larger sand particles can weaken 5Y-TPZ.

The biaxial flexural strength of 4Y-TPZ and 5Y-TPZ increases with Al_2O_3 sandblasting contrarily to highly translucent zirconia of 6Y-TPZ, a rise directly correlated with the composition of the ZrO_2 phase and microstructure of the zirconia grades. The balance between subsurface microcracks and building up surface compressive stress determines the influence of Al_2O_3-sandblasting on the biaxial flexural strength.[102] Alumina-blasting pressure of 0.20 MPa has been suggested as the most effective for reliable and durable bonding performance of translucent zirconia in conditions of long-term water storage (150 days).[103] As an alternative to conventional alumina-blasting, the silica coating (Cojet® system) can be used as surface treatment for zirconia to improve the shear bond strength of an MDP (methactryloyloxydecyl dihydrogen phosphate)-containing resin cement by promoting both surface roughness, coupling micromechanical retention and chemical bond,[104] throws ionic and hydrogen bonding between 10-MDP and zirconia.[105]

Chemical Modulation by Silan Coupling Agents

Silane coupling agents are compounds containing functional groups that bond with both organic and inorganic materials, act as intermediaries that bond organic materials to inorganic materials, and act as primers for silica-based ceramics.

Chemically, silanes are synthetic organic silicon compounds that are divided into functional and nonfunctional types. Functional silanes have reactive functional groups at both molecular ends that can react with two chemically dissimilar surfaces (Figs. 12-14).

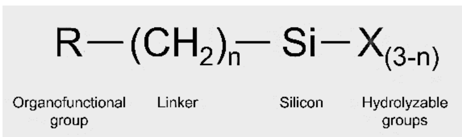


Figure 12 - General formula for a silane coupling agent

The accepted chemical bonding to zirconia depends on the bonding with the phosphate monomer [10-methactryloyloxydecyl dihydrogen phosphate] (MDP), which forms various types of chemical bond with zirconia surfaces and, by end-end resin, bonds to resin cement providing significant bond strength values under specific conditions.[105-107] MDP molecule with a long linear alkyl chain and phosphoric acid ester group, interacts chemically with the hydroxyapatite in the tooth intensively and stably.[108]

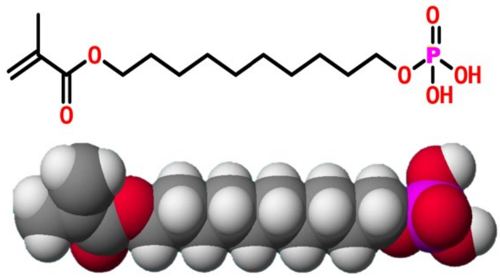


Figure 13 - Linear representation and three-dimensional model of MDP

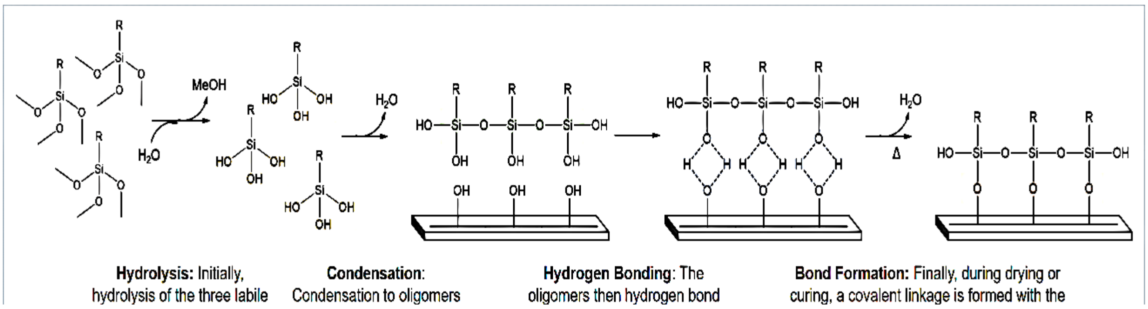


Figure 14 - Silane hydrolysis mechanism during adhesion mechanism of resin bonding to silica-coated substrates (adapted from Matinlinna et al)[109]

Over time, the oral environment promotes bond degradation between substrates[109,110] by hydrolytic cleavage of the siloxane bond in the interfacial siloxane layer. The incorporation of a cross-linked silane into a system with a functional silane improves the bonding and hydrolytic stability of interfacial siloxane links between the resin composite and zirconia.[111] Cross-linked silanes promote the interconnection of functional silanes with the formation of an extensive three-dimensional network that requires more energy to be disrupted. As the siloxane cross-linking density increases the diffusion of water molecules into the network decreases, improving the hydrolytic stability of resin bonding.[110]

Luting cement

Over the past decade, the prevalence of and demand for all-ceramic restorations have increased to meet the esthetic demands of patients. Resin cement has become more prevalent in the cementation of tooth-colored restorations. Given that true universal cement is not yet available, it is the responsibility of the clinician to assess the preparation of the tooth and the characteristics of indirect restoration to make the best selection of cement.[78,112,113] Except in the case of zirconia polycrystals, adhesive luting reinforces the mechanical properties of dental ceramics used as restorative materials.[83]

Polymerization and curing units

Despite the very low thickness of the adhesive interface, such as for direct restorations, light cure factors such as the type of light irradiance, irradiation time, intensity, mode, distance to the material surface, light cure unit conditions and the compatibility between light wavelength and photoinitiator compounds affect the polymerization of the organic matrix of resin composites and facilitate the release of bisphenol-A (BPA).[114,115] The amount of light transmitted through resin matrix composites is influenced by the size, content, microstructure, and shape of the inorganic filler particles. The decrease in the degree of conversion negatively affects the physical and mechanical properties of resin-matrix composites.[114] Optimal light cure parameters result in low release of monomers and minimal toxicity to the dentin-pulp complex, mucosa, or periodontal tissues.[115,116] This aspect is pertinent because the release of these monomers must be added to those released from restoration itself whenever a resin-based CAD/CAM material is used, except Vita Enamic (ENA),[117] probably due to its particular structure.

Mechanical properties are most affected by the type of material, whereas differences in curing conditions seem less influential.[118]

To overcome the distance between the light curing unit and the interface to be cured, a dual-cure resin cement can be suggested for cementation, especially for restorations with thicknesses of 1.5 mm and above.[119] Even so, dual-cure cement should be optimally light-cured to maximize mechanical properties.[118]

Operatory Field Isolation

Despite some controversy,[120] rubber dam operatory field isolation, should be routine during bonding,[121,122] an attitude that requires a change in the paradigm of indirect cementation.[123,124] Rubber dam isolation has a significant effect on bond strengths to enamel, independent of the adhesive system.[122]

2.4 Bonding to different adherends (substrates)

2.4.1 Bonding to Enamel and Dentin

The 3-step system (etch-and-rinse adhesive system) is considered the most effective given its lower risk of hydrolytic degradation at the interface level. It is still the gold standard for cementing indirect restorations.[125] However, it is a highly sensitive technique, mainly in terms of humidity control during the procedure.[92,125]

Despite the favorable reduction in clinical time, self-etched adhesive systems are more prone to degradation at the interface level, because of their behavior as permeable membranes.[92,125]

Recently, universal adhesives with easier adhesive protocols have been introduced by the industry. Research results show that enamel bond strength improves with an initial selective enamel etching with phosphoric acid, but this effect was not evident for dentin using mild universal adhesives with the etch-and-rinse strategy.[126] Due to the presence of acidic and phosphoric monomers in the formulation, separate conditioning of dentin surfaces with primers is not recommended, and self-adhesive resin cements are equally effective alternatives to conventional resin cement.[127]

Regarding the etch-and-rinse adhesive and self-etch adhesive systems, some modifications to the manufacturer's instructions can improve overall bond strength.[78,128] The application of a hydrophobic resin layer, extended application time, application assisted by an electric current, double layer application, agitation technique, and active application of the adhesive are some of these modifications.[92,128] The in vitro evidence suggests that alternative techniques or additional strategies to the application of adhesive systems can improve their bond strength to dentin.[128]

Owing to ethical restrictions regarding the use of extracted human teeth for research purposes, bovine teeth can be used. Bovine enamel shows similar hardness, higher fracture toughness, and higher crack repair capability than human enamel, but the chemical composition of both types of enamel is similar, making bovine enamel a suitable alternative to human enamel for in vitro testing of dental biomaterials from mechanical and chemical perspectives.[87,129] These findings suggest that the factors that interfere with the quality of adhesion to bovine teeth are similar to those of human teeth; therefore, the same adhesion protocols should be valid.

2.4.2 Bonding to hybrid ceramic

The hybrid ceramic material is based on a polymer-infiltrated ceramic network material that consists of a dominant ceramic network reinforced by an acrylic polymer network resin, with both networks fully penetrating one another.[41] Following recent recommendations of the International Academy of Adhesive Dentistry, available in vitro studies found that hydrofluoric acid (HF) etching in combination with silane to be a superior pretreatment with no further treatment before luting.[130,131] However, the best protocol is far from well established, and the combination of sandblasting with a universal multipurpose primer can be used for successful bonding.[20,78]

2.4.3 Bonding to glass-matrix ceramics

The gold standard procedure for adhesive cementation of glass matrix ceramics involves HF etching and silanization,[41] but more recently the procedure with a self-etching ceramic primer was described with similar efficacy and simpler protocol.[20,90,91,132] Nevertheless, this last procedure seems to be more material dependent in terms of etching efficacy and bonding performance, still raising some controversy,[89,133] and it was argued that universal adhesive systems that do not contain a silane should be avoided for bonding lithium disilicate ceramic restorations due to their inferior bond strength.[134]

Different concentrations of HF have been proposed based on ceramic composition, and several etching durations can be recommended, with a tendency to use higher concentrations (10%) for a shorter time (< 30 seconds).[86,88,90] The glass components are selectively dissolved HF, resulting in micro irregularities of the surface and an increase in micromechanical retention.[41,135] IPS® Empress CAD (Ivoclar Vivadent), IPS® e.max CAD (Ivoclar-Vivadent), Celtra® Duo (Dentsply), VITABLOCS® Mark II (VITA-Zahnfabrik), Paradigm™ C Ceramic Blocks (3M ESPE), VITA SUPRINITY® PC (VITA-Zahnfabrik), are some of that kind of material commercially available.

Despite the possibility of more conventional cementation with glass-ionomer cement, in particular those that incorporate nanotechnology, adhesive cementation favors the compressive strength of zirconia-reinforced lithium silicate ceramic.[113,136]

2.4.4 Bonding to zirconia

The achievement of a reliable bond between zirconium oxide material and resin cement is an old and still challenging problem, even with time-consuming protocols or protocols that require complicated and technique-sensitive procedures.[137-140] The bond is essentially micromechanical despite a possible chemical bond when an MDP-based luting cement or adhesive system is applied.[105,107]

The adhesion of the luting cement to zirconia, as with other materials, is significantly influenced, among other factors, by the surface conditioning method and cement type, and the physicochemical conditioning of zirconia and the use of MDP-based resin cement is expected to increase adhesion.[107]

Solutions containing MDP, associated or not with an MDP-containing universal adhesive for bonding to air-abraded zirconia provide stable adhesion after thermocycling.[141] Universal adhesives generate higher bond strengths compared to conventional zirconia primers.[92,113,142]

A mixture of these two concepts was presented,[103] as a combination of 10-MDP containing primers or resin cement and alumina abrasion at 0.20 MPa to provide durable and reliable bonding to Y-TPZ zirconia ceramic. Interestingly, those authors[103] found that when the alumina blasting pressure was lower, higher, or not present, no durable bonding to zirconia ceramic was achieved regardless of using 10-MDP containing adhesives, which reinforces that, in addition to selecting an appropriate cement system, optimal bonding to zirconia requires optimization of the sandblasting pressure,[103] raising doubts about the transposition of laboratory findings into clinical context because the equipment available in clinics is rarely similar to that used in the laboratory.[20]

Others state that if conventional composite resin cement contains phosphate monomers such as MDP, it is not necessary to pretreat zirconia with a phosphate-containing adhesive system.[37] It has also been proposed that the deposition of crystalline hydroxyapatite nanoparticles on the surface of zirconia ceramic improves the quality and values of bond strength when luting with a self-etching dual-cure fluoride-releasing cement with MDP for universal use.[28]

To bond zirconia, it was suggested to use airborne particle abrasion with 50 µm alumina (Al_2O_3) at 0.1 to 0.25 MPa in combination with a phosphate monomer-containing adhesive resin until further studies become available,[121] what is slightly different from another proposed protocol with alumina particles from 30 to 50 μm, at a pressure between 0.05 and 0.25 MPa with a duration of at least 20 s.[107] In fact, the better protocol is far from being well established and sometimes is unknown or misused by clinicians and prosthetic technicians, due to a lack of knowledge update or slowness in technological updating.[20]

Another concern is the zirconia yttria content, as pre-cementation procedures can affect the load at fracture and cement retention of dental zirconia, so some authors proposed that air-abrasion should be used for zirconia with moderate yttria content (< 4 mol%/3Y), but acid etching with heated potassium bifluoride (KHF_2) for enhancing retention on zirconia with higher yttria content (> 5 mol%/5Y).[143] However, they described the acid etching with heated KHF_2 as a complicated process, so air abrasion with Al_2O_3 remains the better option, keeping in mind that pre-cementation procedures need to be adjusted for the different dental zirconia materials to optimize both strength and retention.[143]

2.5 Adhesive systems and adhesive cements

Dental adhesive systems are complex chemical mixtures influenced by the presence and quantity of any component. The type and ratio of monomers, solvents, and initiators present in the mixture affect the physicochemical properties and bonding efficiency to tooth substrates, conditioning their proper clinical application in each clinical case.[144] Various adhesive systems are available to bond resin cements to restorative materials and tooth tissues. These systems can be broadly classified into three categories: etch-and-rinse, self-etch, and universal.[145] Regardless of the strategy used, the removal of residual water from the tooth surface is fundamental to avoid hydrolytic degradation and loss of bond strength over time.[110]

Long-term clinical data on resin bonding of partial-coverage high-strength ceramic or monolithic zirconia restorations are still missing.[146] However, high-strength ceramic resin-bonded bridges (RBBs) are expected to have high long-term clinical success rates, particularly when designed as cantilevers with only one retainer, as is the case for MLIA treatment.

However, a study that evaluated RBBs with different metal framework designs concluded that a fixed-fixed framework (3-unit bridge) showed the highest tensile bond strength and that cantilever single-abutment RBB had the least bond strength, encouraging careful case selection and meticulous treatment planning to achieve long-term survival of the prosthesis.[147]

In an attempt to connect laboratory results to clinical performance, some authors reviewed the literature and concluded that with correctly designed buccal and lingual coverage retainers and minimal if any veneering porcelain, zirconia-based posterior inlay-retained RBBs appear to have a high clinical survival rate; however, the role of bonding efficacy in this survival rate remains unknown.[121] Furthermore, the 3-unit anterior cantilevered zirconia RBB appears to have a high clinical survival rate. Although these prostheses can debond, a catastrophic fracture of the entire prosthesis seems unlikely, so they may be rebonded.[121] Nevertheless, we must be conscientious of the psychological negative effect that a debond can have on the self-esteem of a patient already psychologically traumatized by an MLIA, even if it occurs for a short period.[2,3]

When selecting an appropriate adhesive system, the clinician must be aware of the choices available on the market and the coexistent lack standardized classification.[20]

The use of zinc phosphate and glass ionomer cement for full metal and metal-porcelain restorations has long been accepted. Nowadays, with the most popular restorations based on composite and ceramic materials, the three most used cement types are glass ionomer cement, resin cement, and a combination of both, resin-modified glass ionomer cement.[113,145]

2.5.1 Compatibility with luting cements

The possibility of eliminating the rinsing step makes the combination of a self-etching bonding system with a luting cement attractive, but before use a compatibility assessment should be done.[92,148] Different adhesives cannot be arbitrarily combined because they might be incompatible.[149] The two-step self-etch adhesive system seems to be more reliable than the one-step self-etch adhesive system.[148,149] The incompatibility between the self-etch adhesive system and the self-curing resin composite cement is related to oxygen inhibition and amine neutralization through acidic monomer, but also with the individual components of adhesives, the degree of water removal from the adhesive, air drying,[148,149] and the effectiveness of cross-linking between adhesive polymers.[110] They also frequently form a discontinuous, irregular, and shallow hybrid layer associated with low wettability, viscosity of the system, and low infiltration into dental tissues.[125]

Self-etching adhesive systems concerning performance and clinical indications are material dependent, a relevant detail noticed since they were introduced to be used as auto-cured and dual-cured composites to bond indirect restoration and core build-up restorations on damaged teeth.[125]

A light-cured filled matrix-resin composite coupled with an adhesive system can also be used to bond porcelain or resin composite veneers, instead of a resin luting cement, because composite material can provide sufficient bonding strength to the tooth structure while also being able to closely match the color of the veneer material.[113,150]

However, when bonding all-ceramic restorations to teeth with short clinical crowns, it is generally recommended to use an adhesive luting cement rather than a composite material, because adhesive luting cements allow for superior bonding strength and are better able to withstand the stresses of biting and chewing.[79,82] Furthermore, when using self-etch systems for bonding, it is important to note that the acidic monomers present in these systems can affect the polymerization of dual-cured and self-cured resins, leading to weaker bonds and potential failure of the restoration.[83,145,151]

It must be mentioned that immediate dentin sealing (IDS) should be used whenever possible, [20] and that single-visit indirect restorations should be preferred to multi-visit ones.[78]

Conscious selection of the cement used to retain each type of restoration/material is necessary to reduce potential complications and ensure predictable successful treatment.[152]

The clinician must follow the manufacturer's recommendations before using multiple different systems, although the recommended protocol can sometimes not be the best performing for that specific material, but randomized clinical trials still lack.[78] The recent trend of using self-adhesive luting resins may change the clinical vulnerability of using incompatible systems.[20]

2.5.2 Luting agent selection

Valid selection of the luting agent is crucial for the longevity and success of indirect restorations. This is a challenging decision due to the increasing number of restorative materials, adhesive systems, and luting agents.[20,113] This calls for the need to identify the best properties of a luting agent for indirect restoration bonded by dental resins, but also the clinician's awareness of variation in dental tissue and individual bonding technique strategies.[153]

A luting cement must provide a durable bond between the restoration and the tooth, and simultaneously wet the tooth and restoration surface, and exhibit adequate film thickness and viscosity.[92,154]

Biocompatibility, good mechanical, esthetic properties, easy handling, low solubility, anticaries activity, adequate radiopacity, and cost-effectiveness are also expected characteristics.[155]

Each type of cement has unique characteristics, advantages, and disadvantages. The selection of an appropriate cementation mode is affected by the characteristics of the restoration, the clinical covariables, and the properties of the used material.[146]

If esthetics is not an issue, for zirconia polycrystals a resin-modified glass-ionomer approach is possible because this type of material has the unique properties of self-adhesion to the tooth tissue.[113,145]

The advantages of resin cements in general, apart from their ability to adhere to cementation, are their excellent physical properties.[113,145]

Compared to water-based cements, they generally exhibit high flexural strength, diametral tensile strength, modulus of elasticity, fracture toughness, and hardness.[46,125,156]

Furthermore, they show high compressive strength values, high fatigue resistance, are virtually insoluble in the oral environment, and have improved marginal wear resistance compared to resin-modified glass ionomer cement.[157]

The ability to adhere to restorations has significant advantages, when the tooth preparation obtained for an indirect restoration does not provide the desired macromechanical retention.[158-160]

Etch-and-rinse resin cements (3-step adhesive strategy)

Resin luting cements have chemical components similar to those of the resin-matrix composite filling materials. Lower viscosity makes them easier to apply in thin layers and increases wettability, allowing easy flow into microscopic irregularities of the restorative material and tooth structure, improving their bonding strength.[145,151]

Etch-and-rinse systems involve the use of an acid etchant (35-40% phosphoric acid) to prepare the tooth surface, followed by the application of a bonding agent.[92]

Bonding to enamel occurs through the interlocking of the resin with the hydroxyapatite crystals and rods of the etched enamel, as described same decades ago by Buonocore.[24]

At the dentin level, the etchant dissolves the smear layer produced during tooth instrumentation, creating a rough surface that enhances the bonding of the resin cement to the tooth. The gaps created by the etchant are then filled with the bonding agent forming a micromechanical bond with the tooth structure, in the form of a hybrid layer or resin-dentin interdiffusion zone.[92]

Self-adhesive resin cements

Self-adhesive cement (SARC) adheres to tooth substrates, without the need for pretreatment, based on acid-functionalized methacrylate or related monomers incorporated in these cements for direct bonding to tooth tissue through a polyacid matrix structure.[92]

The lack of a separate adhesive system improves clinical acceptance and straightforwardness. Although marketed as resin cement, these products are hybrid materials that combine the etching and bonding steps into a single application, features of self-etching adhesives and resin composites.[113]

However, laboratory tests frequently found that SARCs used isolated have worst performance compared to the same self-adhesive cement plus etching, therefore recommending the traditional adhesive protocol (acid etching and application of the adhesive system followed by the cement), especially in cases with a short residual crown or functionally challenging clinical situations.[78,91,113,121,145] However, conditioning with 37% phosphoric acid for 15 s increases the adhesion of the self-adhesive resin cement to the dentin, regardless of the use of the dental adhesive system.[78,161]

The polymerization reaction of a SARC is based on the cross-linking of monomers with functional groups of phosphoric acid, which bind to calcium in hydroxylapatite to form an attachment between the methacrylate network and the tooth, with pH neutralization.[162]

When adhering to dentin, the bond strength values seem to be between those achieved with a traditional adhesive protocol (3-step adhesive strategy) and a glass ionomer cement, which is in line with the expected values based on its chemical formulation.[92,113,144] The bond strength to enamel is more challenging with these materials and should be more explored.[78]

Universal adhesives and resin cements

Universal adhesive systems offer the flexibility to use either the etch-and-rinse or self-etch technique or selective enamel etching, depending on the clinical situation. Therefore, they are known as 'universal' or 'multi-mode' adhesives.[163] Meanwhile, 'universal' also means to be used with a variety of restorative materials, associated with silanes for ceramics and indirect composites, or with adhesive primers for metal alloys and zirconia oxide. In addition, they are recommended for a multitude of clinical situations (direct restorations, indirect restorations, resin coatings, core buildups, zirconia priming, and tooth desensitization).[164] A similar philosophy is transposed to universal cements.

A disadvantage of conventional non-self-adhesive resin cement is its high technique sensitivity, including the need for well-controlled clinical circumstances regarding isolation,[80,126,128,145] since most adhesive systems are adversely affected by humidity.[92] Their technique sensitivity is illustrated in studies reporting significant differences in bond strength

between operators performing the same bonding procedure.[165,166] This may widen the gap between their performance under ideal conditions in the laboratory and in everyday practice.

Bisphenol A (BPA)-free luting cements

Most dental materials contain BPA derivatives, such as bisphenol A-glycidyl methacrylate (Bis-GMA) and bisphenol A diglycidyl methacrylate ethoxylated (Bis-EMA), and luting cements are no exception. Considered an endocrine disruptor, BPA is long-term released from restorative composites and resin-modified glass ionomers in dependence on the organic matrix content and the polymerization procedure.[115,167]

Although the BPA released from these materials is substantially lower than current limits, even at low concentrations below 0.02 ppm, BPA toxicity should not be excluded and contribute to daily exposure.[168] On the other hand, no exposure should be dismissed as safe, because the effects of BPA on human health have not been fully clarified to date, especially the potential harm of long-term exposure.[115,167]

Low-viscosity resin-matrix composites, which is the case for luting cements, have higher proportions of organic matrix compared to traditional resin-matrix composites.[115]

Due to human health and environmental issues, some dental manufacturers have developed BPA-free luting cements, which may be a safer option for patients concerned about the potential health effects of BPA. However, it is important to note that there is still much research that needs to be conducted in this area to fully understand the potential risks associated with BPA in dental materials.

ACTIVA BioACTIVE Cement (Pulpdent, Watertown, MA, USA) is based on silica glass particles and an ionic-based resin matrix with calcium, phosphate, and fluoride ions contains no bisphenol A, bis-GMA, or BPA derivatives accessible on the market. The manufacturer proposed it as a dynamic material that reacts with changes in pH in the mouth. It stimulates mineral apatite crystal formation at the material-tooth interface, acting like a smart material, as it continuously releases and recharges its ionic components and actively participates in ionic exchange with saliva and tooth structure.[169] It is self-adhesive, moisture-tolerant, and indicated for indirect applications.

Despite the marketing literature, some studies have put in doubt those properties, as it was found that, for being efficient, at least similarly to other luting cements containing bisphenol A, it should be applied to dentin with a bonding agent.[157] Still, research data are contradictory, as other authors found a similar performance compared to a total-etch (etch-and-rinse) adhesive.[160]

2.5.3 Adhesion of the Restoration

High-quality adhesion between artificial materials and natural teeth has been a pertinent and always present subject since Buonocore[24] in 1955 brought to light the necessity to alter the surface of substrates before adhesion.

Many luting agents are available on the market. Still, nowadays, for single-retainer RBB, scientific evidence supports the use of resin cements, which ideally will achieve biomechanical and biochemical bond simultaneously to the restoration and the almost unprepared tooth, filling the gap between the two joint components.[151,170,171]

Recently, dual-cured, self-etching, and self-adhesive resin cements that do not require bonding agents have been introduced. Furthermore, resin cements are chemically bonded to resin composite restorative materials and silanated porcelain.[154,156,172]

Concerning microleakage, it is plausible to assume that luting agents with stronger bonds to tooth structure, will also allow less microleakage and less histopathological changes, which has been verified in vitro and in vivo studies.[159,160,173]

Resin-glass ionomer hybrid cements (glass-ionomer cements to which water-soluble polymers or polymerizable resins are added) are described as being as retentive as resin cement and as more retentive than glass-ionomer cement. However, there are some contradictory results[160] due to the differences in the cements used for comparison in the different studies.

Based on the literature, self-conditioning cements show values for dentin bonding significantly lower than those for conventional resin cement.[78,174]

Surface contamination has a negative effect on adhesion and is not yet solid evidence to support a universal adhesion protocol.[94]

Dental adhesive systems are chemically complex, and the improvement of their physicochemical properties and bonding efficiency to tooth substrates is directly influenced by the type and ratio of monomers, solvents, and initiators they contain. In this manner, it is important to know the components and their interactions, which is important for the design of new materials, but also to properly adequate their clinical application in each scenario.[144]

2.5.4 Work and setting time

The ideal working time varies with the specificity of the clinical situation and the level of experience of the clinician. More complex restorations or when multiple restorations are placed simultaneously may benefit from a longer working time, allowing the clinician more time to work with the material before it sets. However, a longer working time can increase the risk of contamination or improper placement of the restoration.[155]

A faster setting time can improve patient comfort and reduce chair time, but also shortens the time for careful handling during placement to ensure proper restoration positioning.[112] Setting time can be influenced by several factors, including cement type, mixing technique, and ambient temperature and humidity.[46]

For conventional luting cements, some strategies, such as using a chilled slab or mixing over a wide area to dissipate the heat of the exothermic reaction, can be performed to lengthen the working time but should be done carefully not to weaken the mechanical properties.[175]

Whenever a resin cement is a choice, it can be chemically cured, dual-cured, or only light-cured, whenever the restoration lack of translucency is not an issue.[176] Light-cured resins have the advantages of increased working time, facility to remove excess, and reduced finishing time.[145] Dual-cured have the advantage of accelerated conversion at the surface and deep setting over time.[113,114]

2.5.5 Mechanical properties

The cement used for permanent high-strength bases requires good compressive and tensile forces. Cements are brittle materials with good compressive strength but are usually worst performers relative to tensile strength. Zinc phosphate, conventional glass ionomers, and resin-reinforced glass ionomers have long been on the market, but there is no doubt that resin cements have higher mechanical performance even in stressful conditions such as pulling

out of zirconia endodontic posts, due to a chemical bonding with a hybrid layer formation with resin tags, compared to just physical frictional retention.[113,177]

Table 3 - Basic properties of the dental luting agents referred (adapted from Heboyan et al. (2023)[145]

	Compressive Strength (MPa)	Tensile Strength (MPa)	Elastic Modulus (GPa) (Dentine = 13.7) (Enamel = 84 – 130)
Zinc phosphate	48 – 133	0.65 – 4.5	19.8
Conventional glass-ionomer cement (GIC)	93 – 226	2.36 – 5.3	11.2
Resin-modified glass-Ionomer cement (RMGIC)	85 – 126	2.53 – 24	6.8
Resin cement	52 – 224	5.07 – 41	11.8 – 16.5

2.5.6 In-mouth solubility and Biocompatibility

Theoretically, luting cement should maintain its chemical properties in the presence of oral fluids throughout the restoration life. Still, most of the cements used in dentistry will disintegrate in the oral environment over time.[112,178] Variations in solubility between the different luting agents are a reality, but this could eventually be overcome by a good fit of the restorations.[150,179]

Additionally, an ideal luting agent should not be harmful to dental tissues. Sensitivity after crown cementations is probably due to microleakage rather than pulpal inflammation resulting from the insult caused by the luting agent. Sealing and protection of the dentine-pulp complex should be done before or during cementation, preventing tubular contamination and thus preventing posterior sensitivity.[150] Moreover, immediate dentin sealing (IDS) improves bond strength.[78,180]

Water-based cements suffer acidic erosion in experimental environments, while resin-based cements tend to suffer hygroscopic expansion caused by water sorption, instead of chemical erosion.[181] However, in experimental conditions similar to intraoral conditions, considerably less aggressive, the erosion behavior of glass ionomer cement was similar to the resin-based cements, contrary to previous laboratory results.[182]

Newer self-etched adhesive systems reduce the time spent in clinical practice, but their behavior as permeable membranes at the interface level makes them prone to more degradation[125] and to water aging in comparison with conventional resin cement[183] as the 3-step system seems the most effective due to its lower risk of hydrolytic degradation at the interface level, but requires strict humidity control as they are highly technique sensitive.[125]

The biocompatibility of resin cements and associated adhesive systems is related to their degree of conversion, and complaints of sensitivity may be due to incomplete polymerization.[116] Reduced cell viability of human cells occurs in contact with resin cement, with significant differences depending on the type of cell and cement material, with greater sensitivity for mesenchymal cells, especially osteoblastic cell lines, and less sensitivity to epithelial and endothelial cells. This suggests that despite the properties and adequate handling of resin cements, their widespread use should be cautious, with an emphasis on the pertinence for complete removal of all cement residues, and correct polymerization.[116,184] The degree of cure is an important variable,[118] with dual-cured cements showing less cytotoxicity than self-cured cements.[184]

To minimize the risk of allergic reactions to resin cements, dentists may perform allergy tests before using these materials,[185] because the risk of adverse reactions is believed to be higher for dentists than for patients. Allergies to resin cements have been reported, but are quite rare, but may occur as a result of an immune reaction to one or more components in the cement. Some of the common symptoms of an allergic reaction to resin cement include redness, itching,[185] and swelling of the gums or other tissues of the mouth, as well as difficulty breathing, hives, and anaphylaxis in rare cases. If a patient complains about an allergic reaction to resin cements, in such a case, the cement should be changed to a conventional glass ionomer cement.[185]

2.5.7 Thin thickness (low viscosity)

Ideally, the luting cement material should have a low initial viscosity to easily flow and allow proper seating of the restoration.[145] The luting space should be kept to a minimum to improve the fit of the restoration, exposing the minimum luting material to oral fluids and minimizing any polymerization contraction stress.[170] An effective luting agent should be able to flow to a film thickness of 30 μm or less.[154,186] The mean viscosity of a luting cement (composite- and resin-based cements) can vary widely depending on the type of material and its intended use (full or partial crowns, inlays or onlays, or veneer cementation). Typically, high-viscosity luting cements have a viscosity between 50 and 100 Pa*s, while low-viscosity luting cements can have a viscosity as low as 10 Pa*s. However, for each luting cement, the viscosity varies with temperature and humidity, as well as with the application method (for example, sonication).[187] In a retrospective clinical study for inlays, onlays, and overlays on posterior teeth, a higher survival rate was found if a high-viscosity material (composite-based cement) instead of a low-viscosity material (resin-based cements) was used.[188] This technique could also be chosen for veneer cementation, because mean values of marginal adaptation of 295 and 315 μm, and 202 μm and 195.5 μm of internal adaptation values, respectively, were found for heat-pressed and CAD-CAM veneers, with some marginal discoloration after 2 years of clinical service, in cases of veneers cemented with a resin-based luting cement.[189]

2.5.8 Radiopacity

Radiopacity is a desirable property of an ideal luting agent that enables clinicians to identify the luting cement, teeth, and restoration. Dental cements must have greater opacity than dentine to detect gaps, secondary caries, overfilling, or underfilling. A luting agent should be chosen as radiopaque as possible[145,155] because it is impossible to detect excess luting agent radiographically if the material is radiolucent.

2.5.9 Anticariogenic Properties

Fluoride is released from certain dental materials, although at different rates and for different durations, depending on the material evaluated.[113,190] Many luting agents have been described as having anti-cariogenic properties, and several of them have been marketed under this pretext.

The fluoride content of a material is not a guarantee of its anti-cariogenic properties, as sufficient concentrations of fluoride must be released over time.[145] The material itself should not suffer from any significant degradation.[150] Glass ionomer cements have been reported to have long-term fluoride release.[191,192] However, even if fluoride is released, it is essential to know the amount of fluoride released from the margins of a well-fitting restoration and whether this amount of fluoride has any significant impact.

Recently, a study revealed that an alkasite-based resin composite has a better recharge potential than a giomer (glass-ionomer cement matrix containing resin components) and conventional glass-ionomer cements, after topically applied NaF gel, but also that the conventional composite evaluated showed no recharge ability.[192] Furthermore, the chemical composition of the overcoating adhesive system influences the fluoride recharge and re-release capacity of each material.[192]

Ion-releasing cement could inhibit demineralization of the surrounding root dentin more than a reference self-adhesive resin cement, although at a lower level than a reference resin-modified glass ionomer cement. They may be indicated for patients at risk of secondary caries around the crown margins.[193]

2.5.10 Ease of manipulation

An essential attribute of any dental material is its ease of use and manipulation. Among conventional luting agents, zinc phosphate appears to be the least technique sensitive and if the specific protocol is followed, long-term success will be achieved.[172,175]

Resin cements are extremely technique-sensitive, especially those with a 3-step adhesive strategy, due to their inherent polymerization shrinkage and sensitivity to moisture.[112,122,145] Resin-modified glass ionomer cements are less technique-sensitive than resin cements and, in auto-mix cartridges, are a highly efficient way of delivering cast restorations.[112] This delivery mode is also the best choice when using resin luting cements.

2.5.11 Esthetics

The translucency of all-ceramic restorations, especially anterior restorations, makes the esthetic characteristics of the adhesive cement critical.[172,175]

Esthetic appearance of luting materials is necessary in all non-metallic restorations, particularly when the margins are visible. In such regions, resin-based color-matched luting materials are superior to any other type because of their translucency and excellent color matching to dentin and enamel. Ionomer-based luting materials may also have a good color match, but their translucency is somewhat inferior to that of resin-based luting materials.[170]

Therefore, color stability over time should be considered. The amine accelerator necessary for dual polymerization can cause the color of the luting agent to change with time.[145,194] Therefore, many practitioners prefer light-cured resin cements for the luting of porcelain veneers and other esthetic restorations because it is believed to be more color stable.[145] Light-cured resin cements should also be preferred for the long-term color stability of full ceramic restorations.[194] However, it has been suggested that the color stability of resin cements could be improved.[195]

For translucent restorations made of third- or fourth-generation zirconia, it is recommended not to use an opaque luting material in the visible area for esthetic reasons.

CHAPTER 3
LABORATORY TESTING OF POTENTIAL MATERIALS FOR RESIN BONDED BRIDGES IN THE TREATMENT OF MLIA

3 Laboratory testing

3.1 General aspects

This chapter is presented in a mixed format with descriptive sections and resumed original articles.

The adhesive protocols used were based on the manufacturer's instructions and scientific evidence whenever no experimental conditions were tested. Laboratory procedures were carried out according to evidence-based daily clinical practice, except if the materials required handling in the prosthetic laboratory. In this case, the materials were processed as real RBB ready for use in the mouth. The Stata v17.0 software program (Stata v17.0; StataCorp, Lakeway, TX, USA) was used to perform data analysis whenever applicable.

3.2 Tests for the mechanical characterization of the bonding interface

Several tests are available to characterize the bonding strength of different adhesives or surface preparation methods used to bond monolithic ceramics, depending on the specific application and bonding material used.

The most commonly used methods for evaluating dental materials are (a) the **tensile test**, which involves applying a force perpendicular to the bonded interface, causing the bonded parts to shear apart; (b) the **shear test**, which involves applying a force parallel to the surface or the bond line of the material, causing the materials to slide against each other until they shear or deform; (c) the **flexural test**, which involves the application of a bending force to the bond, and the maximum stress at the bond interface measurement; (d) the **peel test**, which involves applying a force parallel to the bonded interface until one of the bonded parts peels away from the other; (d) the **microindentation test**, in which a small indentation is made in the bonded area using a microindentation tester; and (e) **microscopic examination**,

which determines the nature of the failure (adhesive, cohesive, or mixed) of the fractured surfaces, and allows the inference of the strength of the bond.
In tensile or shear tests, the force is applied at a constant rate until the adhesive joint fails and the maximum force required to break the joint is recorded. The strength of the bond is calculated by dividing the maximum force by the original cross-sectional area of the bond area, and the resultant value is expressed in units of stress, such as pounds per square inch (psi) or megapascals (MPa). This value can be used to compare the strength of different adhesives or bonding methods.

Both tests are useful in providing information on the strength of the adhesive bond and how it will perform under different loading conditions, helping to select materials or adhesives for bonding applications that require a high degree of strength and durability, as is the case with RBB in the rehabilitation of MLIA.

TBS and SBS are popular tests for 7 to 28-mm^2 bonded areas.[196] Instead, micromechanical tests can be used to evaluate the mechanical properties of small-scale material interfaces, typically with dimensions in the range of micrometers or millimeters, but require a specialized testing machine equipped with a small load cell, grips, and an optical microscope to visualize the deformation of the specimen during testing. In dentistry, it is often used to study the bonding interface between dentin and restorative materials.

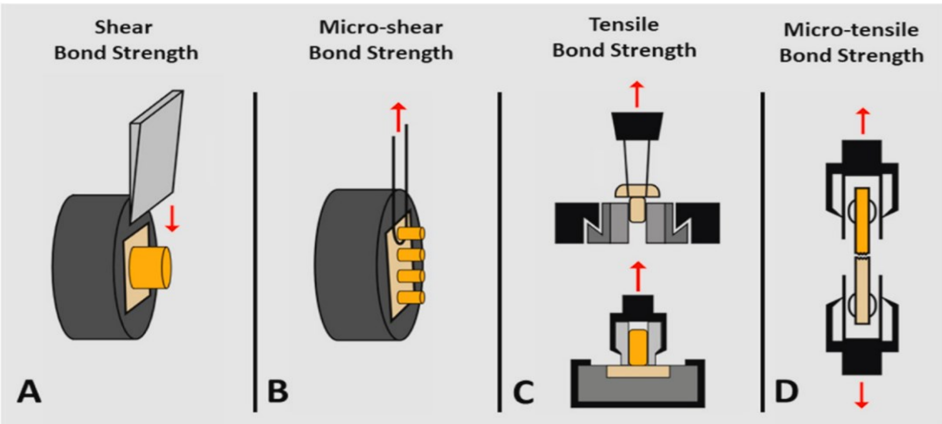


Figure 15 - Schematic illustration of the bond strength tests utilized in the included studies (A: SBS, B: μSBS, C: TBS, D: μTBS). Red arrows represent the direction of applied forces. According to Awad et al[91] under copyright permission from Elsevier.

Concerning the mechanical characterization of bonding protocols for CAD-CAM monolithic ceramics, recently a systematic review and meta-analysis revealed that the type of test performed had no direct influence on the specific comparative results of the adhesive strength assessment for each specific ceramic.[20]

3.3 Main materials used in laboratory testing

Different types of monolithic CAD-CAD ceramics, VITA YZ® [Y-ZPT], VITA SUPRINITY®[SU], VITA ENAMIC®[ENA], from Vita Zahnfabrik, Germany, and three different types of luting cements, Panavia SA Universal Cement® [SA] (Kuraray Europe GmbH, Germany), Rely X Ultimate®[RU], and VITA ADIVA IA-Cem® Ultra opaque [IA] (Vita Zahnfabrik, Germany), were used in this study. Other materials used were Monobond Plus® (MB) (Ivoclar Vivadent AG, Liechtenstein), universal silane; VITA ADIVA C-Prime (CP) (VITA Zahnfabrik, Germany), ceramic primer; VITA ADIVA Ceramic Etch (HF5) (VITA Zahnfabrik, Germany), ceramic etcher; Scotchbond Universal Etchant (PA) (3M ESPE, USA), acid tooth conditioner.

Table 4 lists the main materials and their compositions according to the manufacturer used in **Task 2** (study of the adhesive joint), **Task 3** (testing a new model of RBB specimen model), **Task 4** (natural teeth shear bond strength assessment), and **Task 5** (testing a simulated RBB for MLIA rehabilitation).

Table 4 - General description of the materials used in this study, their compositions, and manufacturers.

Material	Name	Code	Composition	Manufacturer
CAD-CAM Ceramics	VITA Enamic	ENA	86% feldspar ceramics: SiO_2 58–63%, Al_2O_3 20–23%, Na_2O_9–11%, K_2O_4–6% by weight, 14% polymer by weight: TEGDMA, UDMA	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA Suprinity	SU	Zirconium oxide 8–12, silicon dioxide 56–64%, lithium oxide 15–21%, various > 10% by weight	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA 3Y-ZPT	3Y-ZPT	Zirconia reinforced with 3% Yitria	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA 5Y-ZPT	5Y-ZPT	Zirconia reinforced with 5% Yitria	VITA Zahnfabrik, Bad Säckingen, Germany
Renin-matrix restorative composite	PROCLINIC EXPERT Nano Hybrid composite	RES	22.5% weight, multifunctional methacrylic ester; 77.5% weight, inorganic filler (40 nm – 1.5 microns	SDI Limited, Burnston, AUS
Artificial teeth	FRASACO Tooth	FRA	Melamine-based composition	Frasaco GmbH, Tettnang, Germany
Resin composite cement	Panavia SA Universal cement	SA	Paste A: MDP, Bis-GMA, TEGDMA, HEMA, silanated barium glass filler, silanated colloidal silica, dl-camphorquinone, peroxide, catalysts, pigments Paste B: HEMA, silane, silanated barium glass filler, aluminum oxide filler, sodium fluoride (<1%), dl-camphorquinone, accelerators, pigments	Kuraray Europe GmbH, Hattersheim, Germany
	VITA ADIVA IA-Cem Ultra opaque	IA	Mixture of resin based on Bis-GMA, catalyst, stabilizer, pigments	VITA Zahnfabrik, Bad Säckingen, Germany
	RelyX Ultimate	RU	MDP phosphate monomer, dimethacrylate resins, HEMA, Vitrebond™ copolymer filler, ethanol, water, initiators, silane	3 M ESPE, Seefeld, Germany
Etching agent	VITA ADIVA Cera Etch	HF5	Hydrofluoric acid 5%	VITA Zahnfabrik, Bad Säckingen, Germany
	Scotchbond Universal Etchant	PA	Phosphoric acid 35%	3M ESPE, Minneapolis, MN, USA
Ceramic Primer	VITA ADIVA C-Prime	CP	Solution of methacrylsilanes in ethanol	VITA Zahnfabrik, Bad Säckingen, Germany
	Monobond Plus	MB	50–100% ethanol, disulfit methacrylate, ≤2.5% phosphoric acid dimethacrylate, ≤2.5% 3-trimethoxysilylpropyl methacrylate	Ivoclar Vivadent AG, Schaan, Liechtenstein

Bis-GMA, bisphenol A glycidyl methacrylate; HEMA, 2-hydroxyethyl methacrylate; MDP, 10-methacryloyloxydecyl dihydrogen phosphate; TEGDMA, triethylene glycol dimethacrylate; UDMA, urethane dimethacrylate

Specific materials and equipment are detailed in the specific task and in the papers.

3.4 Study of the adhesive joint (Task 2)

3.4.1 Factoring of specimen models and preliminary tests (Task 2.1) (Paper 5)

These initial tests aimed to produce an innovative specimen that could simulate, as much as possible, a partial prosthesis (RBB) adhered with an adhesive cement to rehabilitate a missing lateral incisor in a clinical situation of MLIA.

Despite the fact that there are many different tests in the literature on dental materials that can potentially be used in the rehabilitation of an MLIA situation, few have tested situations designed for the area of the upper lateral incisors. Existing ones were carried out mainly with fixed full-coverage prosthesis crowns, with non-CAD-CAM restorative materials, or with conventional cements.

The preliminary tests were designed to calibrate the procedures and identify constraints. It is worth mentioning that the specimen finally tested in this task was the third attempt at specimen modeling. The first failed due to lack of stability (two Frasaco teeth each inserted into a cast metal support, followed by adhesion of the test cylinder) (Fig. 16 A), and the second due to the unsuccessful standardization of the inclusion of Frasaco teeth in the acrylic resin support, with the buccal surface parallel to each other, to adhere to each side of the cylinder (no intention to abrade the surface of the artificial tooth until the faces were parallel to each other, but to use the surface of the tooth only with the surface treatment of the experimental protocols) (Fig. 16 B). The data acquired with these models were used to make the next model tested in the preliminary tests (Fig. 16 C).

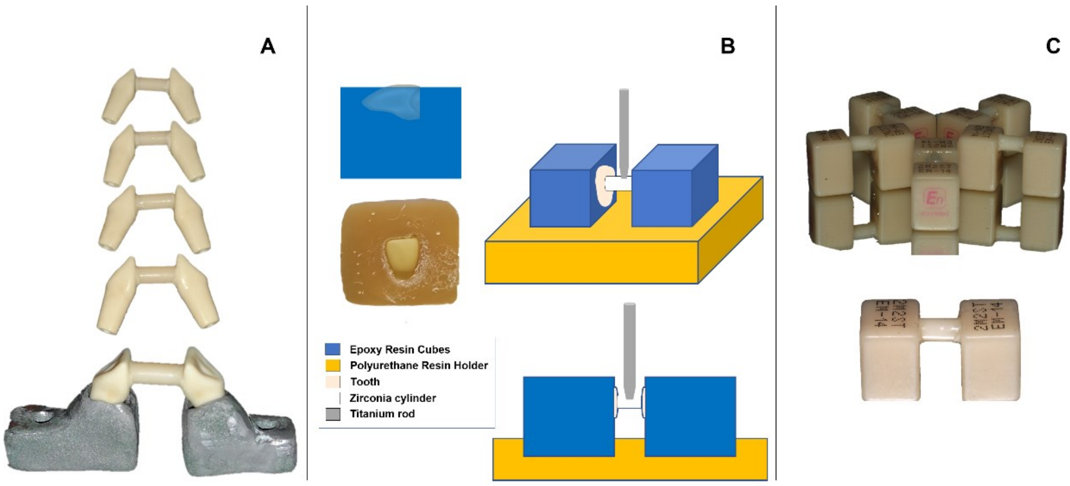


Figure 16 - Specimen models of the first (A) and second (B), and final attempt.

With the third attempt, a prototype of easy replication, stable, and with standardized base adherend was achieved.

Virtual design and 3D printing were used to produce a stabilizer base to reinforce stability. The VITA Enamic block was chosen as the base adherend because of its unique mechanical properties similar to those of the natural tooth. Additionally, the surface treatment recommended for its surface despite being done with another type of acid conditioner is very similar to that recommended for a human tooth. The resilience and toughness of the specimen were intended to simulate those types of characteristics at the level of the periodontal ligament and bone.

Figure 17 shows the experimental protocol. Detailed steps of the experimental protocol are accessible in **Paper 5**.

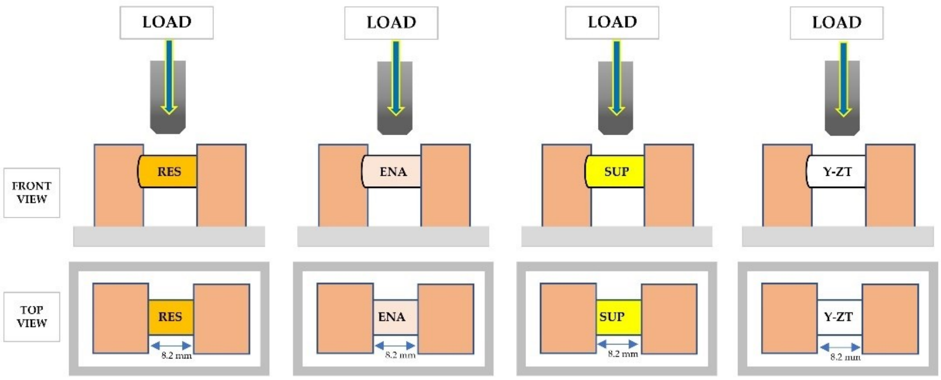


Figure 17 - Experimental protocol for shear bond test

This paper also contains the results of the first in-line study to find a reliable substitute for natural teeth, human or bovine, to overcome ethical restraints and inherent biological variability in future research.

Task 2.1 evaluated the possibility that an experimental specimen model that used a standardized artificial material as a base adherend could be used for the shear bond strength tests of restorative materials. Simultaneously, because the behavior of this material (ENA) for this purpose was unknown, CAD-CAM ceramics with different expected performances in shear bond strength testing were simultaneously evaluated.

Among the CAD-CAM ceramics evaluated as restorative materials, ENA was the easiest to handle. The SUP was very brittle, either in the pre-sintered or sintered state. Y-ZPT had accessible milling procedures, but it was almost impossible to manage the separation of the cylinders after the block had been sintered, having destroyed several diamond burs. In future studies, we highly recommend separating the cylinders before sintering. The resin-matrix composite (RES) was easy to handle, but the possibility of including air bubbles in the cylinder upon production was a concern. The SUP (n=1) and Y-ZT groups had pre-test failures (n=2). Table 5 shows the shear strength by mean and standard deviation, Figure 18 the behavior of the samples under load, and in Figure 19 the box plots the shear strength, with and without preload failures, of the assessed materials. Detailed results are accessible in **Paper 5**.

Table 5 - Shear strength by mean and standard deviation in Newtons and MPa

Groups			Failure load		Shear Strength	
		n	Mean (N)	SD (N)	Mean (MPa)	SD (MPa)
Rely X Ultimate	Resin-matrix Composite	5	843.07	299.82	69.10	24.58
	VITA Enamic	6	224.27	103.82	18.38	8.51
	VITA Suprinity	5	139.56	48.99	11.44	4.02
	VITA Y-ZT	5	225.40	147.88	18.48	12.12

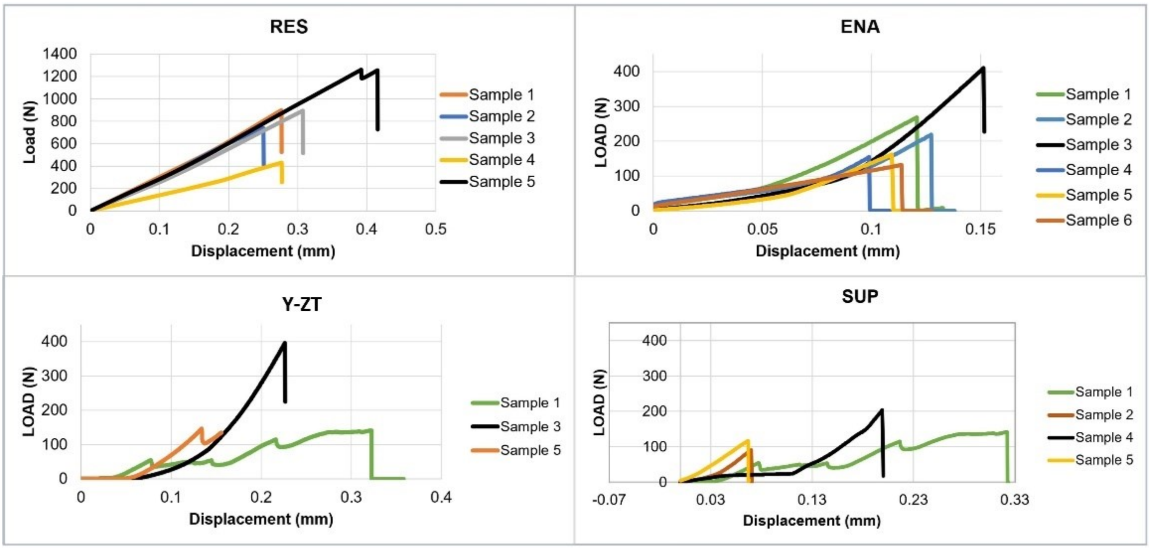


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Figure 18 - Graphic representation of specimen behavior under load of the control (RES), ENA, SUP, and Y-ZT groups

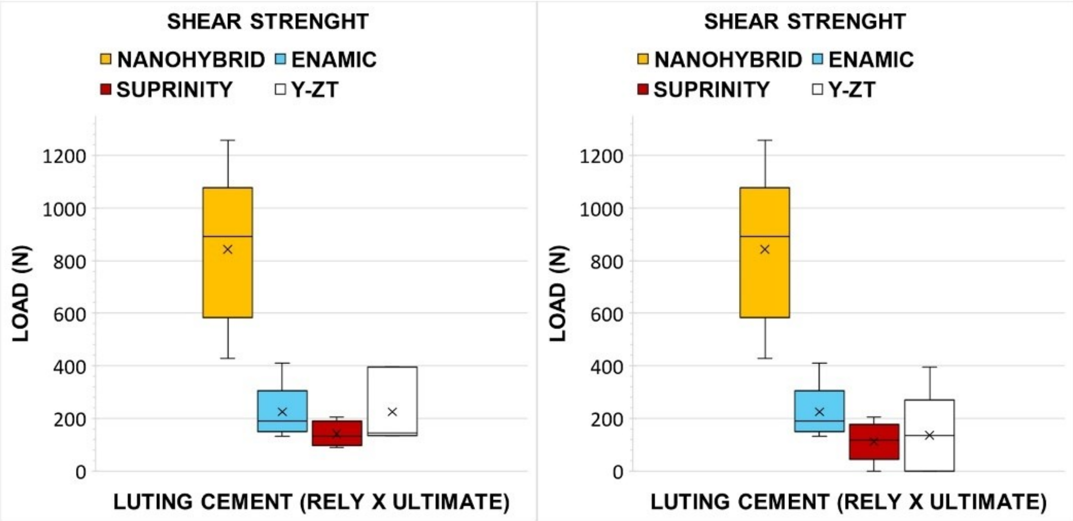

Figure 19 - Box plot of shear strength by restorative material, without preload failures (A) and with preload failures (B)

The SUP and Y-ZT groups were inconsistent before and during loading. The adhesion strength depends on the material. Surprisingly, the RES group performed the best, reaching mean values more than four times higher than the second best, the ENA group.

Based on the parameters depicted in Figure 20, all samples from the Y-ZT group had failed adhesion as a unique mode of failure. In the RES group, the unique failure mode was cohesive, either on the cylinder or on the base, and sometimes simultaneously.

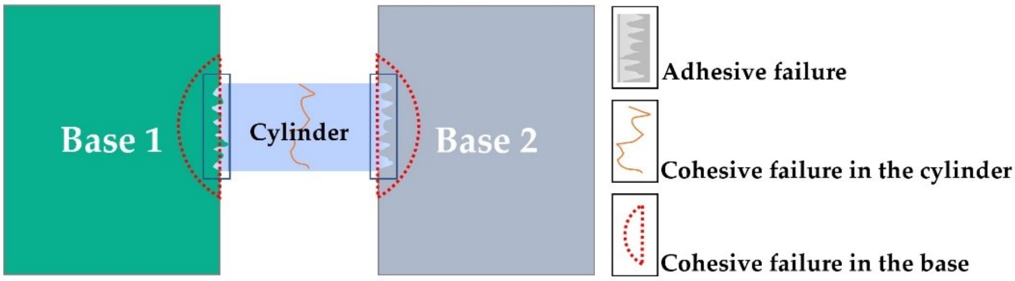

Figure 20 - Comprehensive scheme of the mode of failure

Crossing data obtained from the failure mechanism and surface energy of the different materials evaluated, no correlation was found, indicating that the intrinsic chemical composition of the restorative material and its interaction with the coupling agent were the main factors affecting the mechanical behavior. As can be seen in Figure 21, the three treatments modified the surface of the ENA; the SUP was markedly altered by conditioning with HF 5% for 60 s and only slightly by sandblasting with AL_2O_3 50µ, and Y-ZT was not affected by HF 5%. These findings confirmed the data found in the literature.

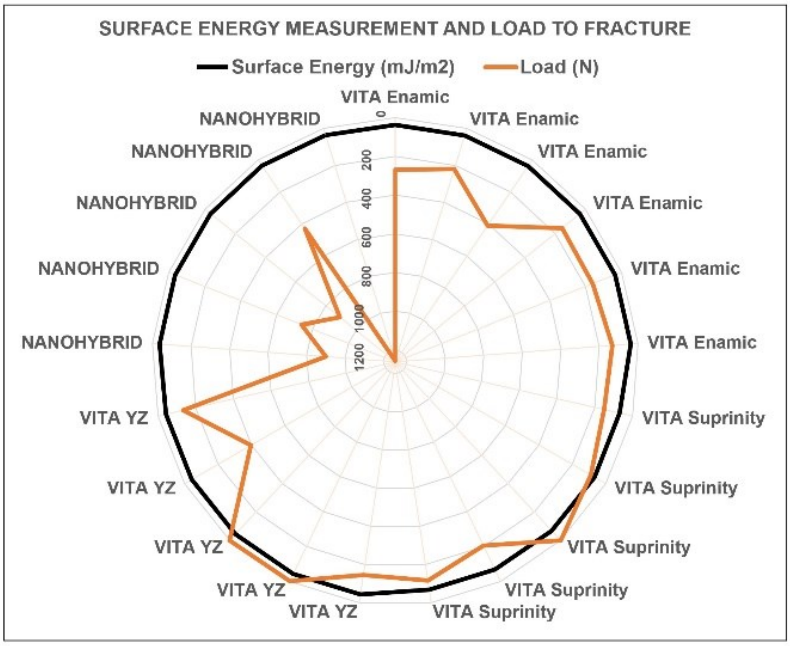

Figure 21 - Radar graph with mechanical performance comparison in relation to the highest surface energy measured by type of CAD-CAM monolithic ceramic

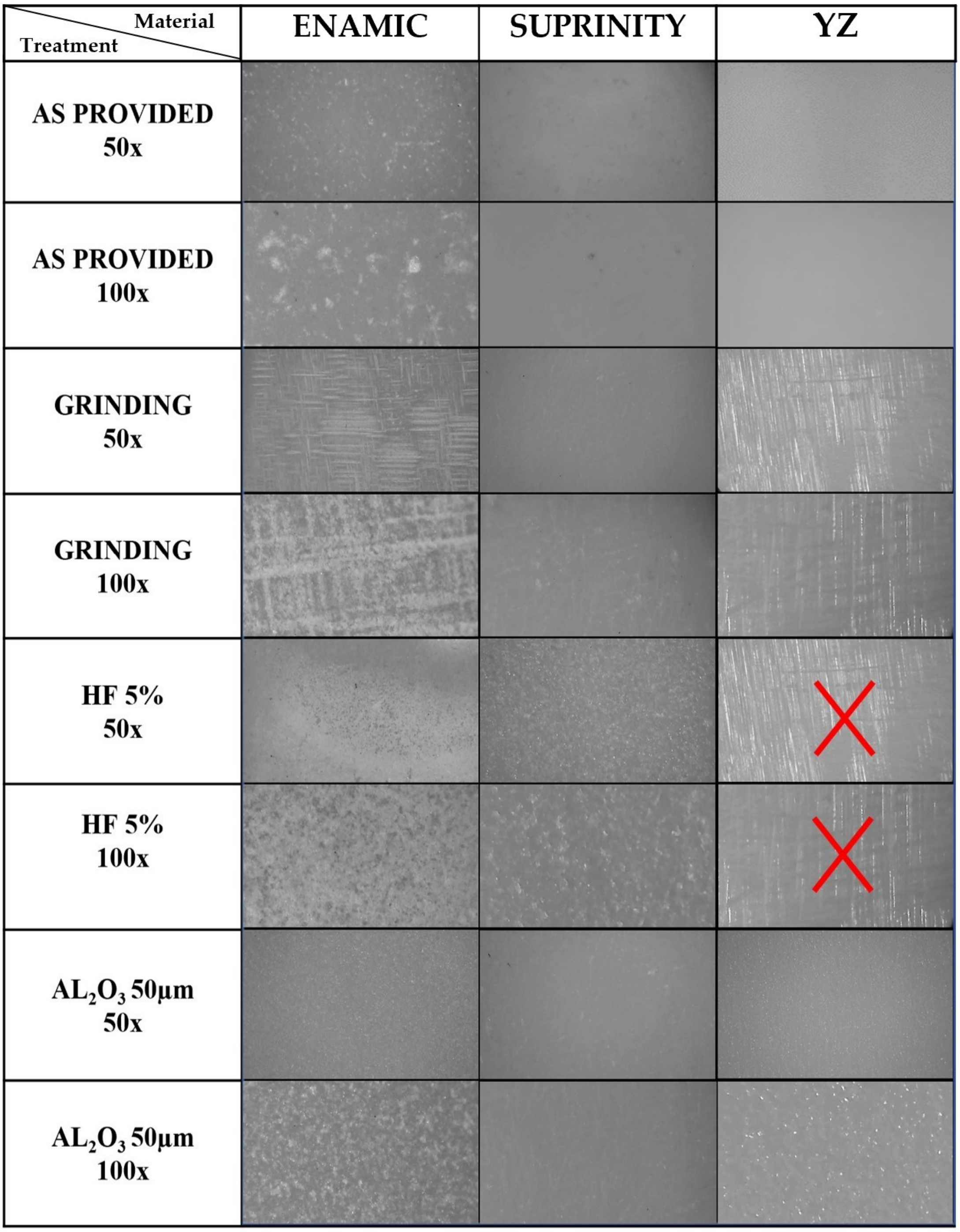

Figure 22 - Microscopy observation (50x and 100x ampliation) of the CAD-CAM ceramics after different surface treatments [as provided by the manufacturer, grinded by coarse disk, 5% hydrofluoric acid for 60 s (HF 5%), aluminum oxide blasting (Al_2O_3 50µm)

Crossing of microscopy and surface energy data shows that HF 5% is a suitable treatment to prepare the surface of SUP for adhesion if we only consider the microscopic interlocking between the restorative material and the adhesive cement. Other materials are dependent on chemical reactions.

Within the experimental conditions of this study, no relationship was found between SBS and the surface energy of the substrates, the failure mode was material dependent, and differences in behavior concerning shear forces were identified between CAD-CAM ceramics. The mode of failure with Y-ZT was always adhesive, highlighting uncertainties about the efficiency of the adhesive joint of this material in the absence of macromechanical retention. The VITA Enamic block resists a shear load of up to 100 MPa (RES sample 5 test) in a design consisting of a cylinder with a double interface connection, so it appears as a potential base adherend for SBS tests.

Another innovation of task 2.1 is the testing of a polymer-infiltrated CAD-CAM ceramic as a potential substitute for natural teeth in shear strength tests. Being an industrially manufactured material, the predictability of mechanical behavior is expected. In addition, because of the mixed chemical composition (polymer and ceramic), a behavior similar to that of a natural tooth as a base adherend is also aimed at testing different CAD-CAM monolithic ceramics. Another peculiarity of this study is that, except for the test equipment, it was carried out with equipment within the reach of a dentist in most countries. Therefore, the clinical protocols were evaluated in parallel. The experimental methodology followed strict control and was reported pedagogically throughout the paper.

Relevance: The findings of this study are the first step toward a reliable substitute for natural teeth to overcome ethical restrictions and inherent biological variability in future research. The results suggest that a polymer-infiltrated CAD-CAM ceramic (ENA) is a potential base adherend for shear bond strength tests of restorative materials, although further research is necessary to confirm its efficacy as an alternative to natural teeth. Furthermore, the findings of this research will allow future studies to compare the mechanical behavior of restorative materials with the same base adherend, which is not possible with natural teeth due to their inherent biological variability. It was possible to identify the major differences between the CAD-CAM materials under the possible load forces in a three-unit RBB.

3.4.2 Modulation of the adhesive interface (Task 2.2) (Paper 6)

This task was developed to evaluate the effect of coupling agents and surface treatment on the shear bond strength of three luting cements adhered to a CAD-CAM ceramic mechanically similar to the human tooth. Detailed steps of the experimental protocol are accessible in **Paper 6.**

Three adhesive cements with different adhesive strategies [Panavia SA (SA), RelyX Ultimate (RU), and Vita Adiva IA-Cem (IA)] were used to adhere as cylinders to VITA Enamic blocks. Block surface treatment was grinding with no further treatment or 5% hydrofluoric acid for 60s. VITA Adiva C-Prime (CP) and Monobond Plus (MB) were the alternative coupling agents. Figure 23 shows some steps of specimen production. The surface energy assessment (block and cement), shear bond strength (SBS), the ultimate tensile strength of each block, and the fracture analyses were performed. SA in the self-adhesive mode adhered to only grinded block was the control group (SA/0). The data was properly analyzed and details can be examined in **Paper 6**.

Figure 23 - Surface treatment with 5% HF and coupling agents. (A) After grinding, (B) conditioning with 5% hydrofluoric acid, (C) air-dried block surfaces after washing with water spray for 60 seconds and (D) application of the coupling agent according to the group. One group was left unconditioned and without coupling agent (control group)

Figure 24 describes and shows details of the mechanical tests.

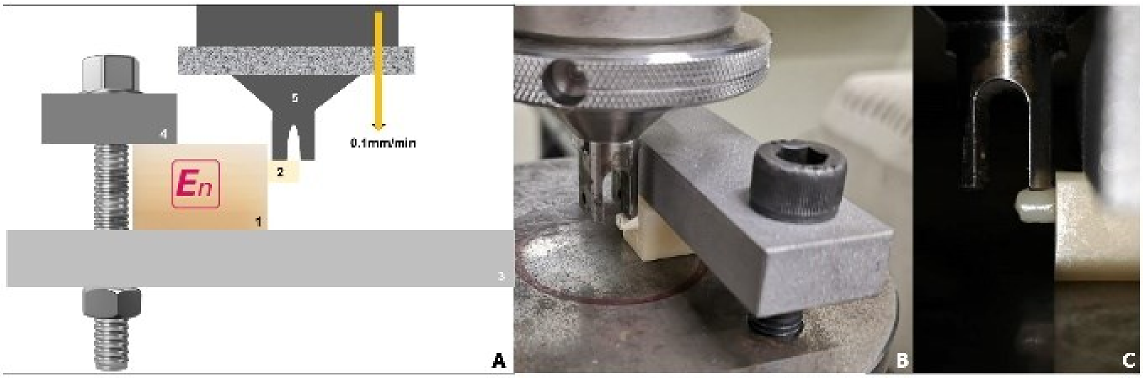

Figure 24 - Components designed for testing (1: ceramic block; 2: cement cylinder; 3: stationary base; 4: block stabilizer; 5: load cell and piston); (B) block stabilized on base and specimen positioned for SBS; (C) piston positioned over the cylinder, 1 mm away from the block

The RU/MB group had the best SBS ($p<.001$). RU (349.12 ± 26.94N) and IA (157.50 ± 21.7N) performed better with MB and SA (221.05 ± 29.99N) with CP. CP (221.05 ± 29.99N) > MB (180.59 ± 20.27N) increased SA SBS compared to self-adhesive mode (SA/0, 119.97 ± 43.05N). The RU/CP association showed inconsistent SBS. No direct influence on SBS was found to be related to the surface energy of the substrates. The polymerization efficacy of IA-Cem raised doubts. The fluorescence of RU was helpful for excess removal.

All combinations tested, except SA / 0, achieved shear bond strength values within those aimed at adhesion to tooth substrates. The coupling agent and cement affected the SBS under the test conditions. RU performed better than the other cements with both coupling agents (MB and CP). Except for SA, the MB performed better as a coupling agent. The VITA Enamic hybrid ceramic block is a potential support for shear tests with luting cement.

Based on the results obtained, the shear bond strength of the adhesive interface between the luting cements and the VITA Enamic block was positively influenced by the use of a coupling agent, either MB or CP, and a specific surface treatment. This suggests that the surface energy of the VITA Enamic block, the hybrid ceramic used in this study, is not enough by itself to promote the adhesion of dual-cured self-adhesive luting cements. This study also demonstrated that the VITA Enamic block is an appropriate substrate for laboratory testing of the shear bond strength of adhesive interfaces between luting cements and tooth-like materials.

CLINICAL RELEVANCE: From this study, we can translate into the clinical context that silanes improve the performance of luting cements but are not a substitute for proper clinical techniques and treatment of the tooth and the restoration surface. The manufacturer's instructions do not always produce the best mechanical performance of a material but should be followed until further information from randomized clinical trials is provided.

3.4.3 Search for an industrial alternative to human teeth (Task 2.3)

In this task, the shear bond strength of an artificial adherend, FRASACO teeth, was evaluated to find a possible anatomical substitute of a human or bovine tooth for shear bond testing. These teeth are produced industrially from melamine, making them a standardized substrate. The possibility of having a cheap and almost over-the-counter material is an attractive idea, and if feasible, would allow the surpassing of several ethical and biological problems.

Frasaco teeth (n=30) were embedded in acrylic resin and cut with a circular diamond saw to produce a flat standard surface. The cutting was done to remove a maximum of 2 mm from the buccal tooth surface. After cleaning with air and water spray, the cubes with the teeth were randomly distributed, followed by assignment in 5 groups (n=6) according to the experimental adhesive protocol to be performed (Table 6). All surface treatments for the experiment followed the procedures already described in the previous tasks.

Table 6 - Experimental groups by adhesive protocol (adhesive cement, surface treatment, and coupling agent)

CEMENT	SURFACE TREATMENT	COUPLING AGENT
Panavia SA (SA_00)	Grinded	None
Panavia SA (SA_AL_0)	Aluminum oxide	None
Panavia SA (SA_HF5_0)	Hydrofluoric acid	None
Panavia SA (SA_HF5_MB)	Hydrofluoric acid	Monobond
Rely X Ultimate (RU_HF5_MB)	Hydrofluoric acid	Monobond

As no literature referred to surface treatment or adhesive protocols performed with FRASACO teeth was found, preliminary tests were performed.

The group was left intact, that is, only grinded. The other 4 were treated with 5% hydrofluoric acid (5% HF), 60 s; 9,6% hydrofluoric acid (9.6% HF), 60 s; aluminum oxide 50µm, 0.25 MPa, 10mm, 10 s (AL) and 35% phosphoric acid (35% PA), 60 s. In Figure 25, some details are shown.

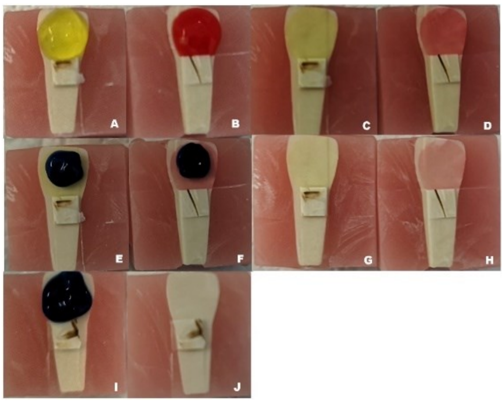

Figure 25 - Different surface treatment of the FRASACO tooth cuted surface. (A, 9,6% hydrofluoric acid, 60 s); (B) 5% hydrofluoric acid, 60 s; (C, D) after washing with undoubtful pigmentation; (E, F) 35% phosphoric acid to the previous etched surface; (G, H) no visible effect of 35% phosphoric acid effect; (I) 35% phosphoric acid, 30 s, as a surface conditioner; (J) after washing with no recognizable effect.

The cylinders were cemented with a protocol similar to that used in Task 2.2, which is detailed in **Paper 6**. In Figure 26 we can see some steps of this execution.

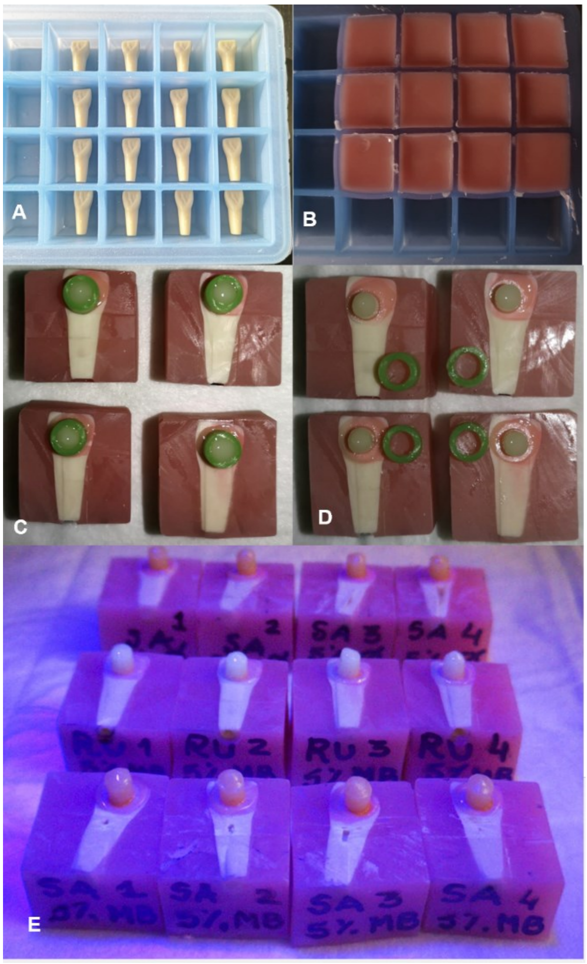

Figure 26 - Fabrication and assembly of samples. (A) teeth positioned in the silicon mold; (B) acrylic resin poured in the mold and waiting full polymerization; (C) cement cylinders waiting to self-cure in the silicon mold, after 5 s photoinitiation; (D) silicon mold removed; (E) violet light incidence revealing the fluorescence of the Rely X Ultimate cement (RU)

Figure 27 shows details of the surface energy measurement and of the shear bond test.

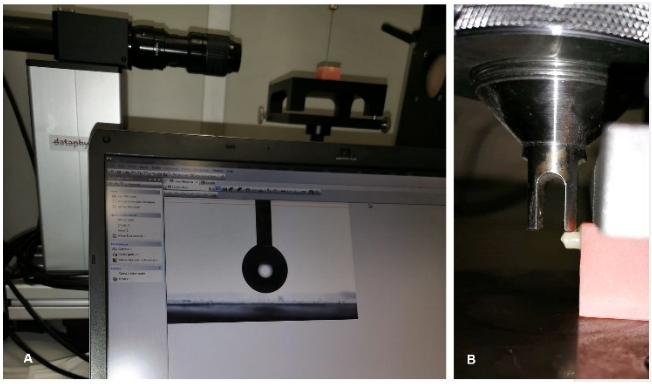

Figure 27 - Surface energy measurement (A) and shear bond test details

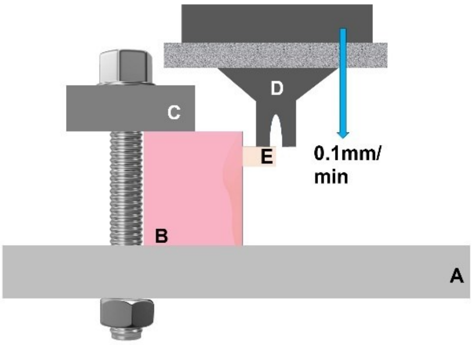

Figure 28 - Schematic representation of the shear strength test. (A) stationary base, (B) acrylic resin block with incorporated Frasaco tooth, (C) block stabilizer, (D) load cell and piston positioned 1mm away from the tooth, and (E) cement cylinder

Surface energy measurements after surface treatment were grinding, 51.41 mJ/m^2; sandblasting, 56 mJ/m^2; 35% PA 58.81 mJ/m^2; 5% HF, 68.55 mJ/m^2; 9.6% HF, 67.73 mJ/m^2. The results of the shear bond tests are shown in Table 7 and are graphically represented in the box plots in Figure 29.

Table 7 – Shear strength by mean and standard deviation in Newtons and MPa

CEMENT	SHEAR STRENGTH		SHEAR STRENGTH	
	Mean (N)	SD (N)	Mean (MPa)	SD (MPa)
Panavia SA (SA_00)	26.66	9.12	4.24	1.45
Panavia SA (SA_AL_0)	58.36	9.95	9.29	1.58
Panavia SA (SA_HF5_0)	35.73	24.30	5.69	3.87
Panavia SA (SA_HF5_MB)	28.59	12.61	4.55	2.01
Rely X Ultimate (RU_HF5_MB)	65.33	15.23	10.40	2.42

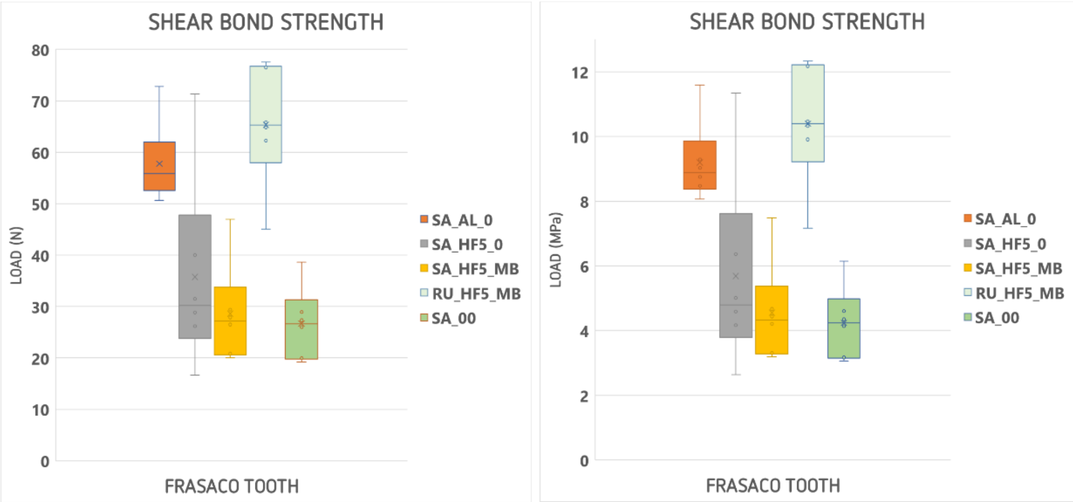

Figure 29 - Shear bond strength of FRASACO tooth adhered to different adhesive cement cylinders

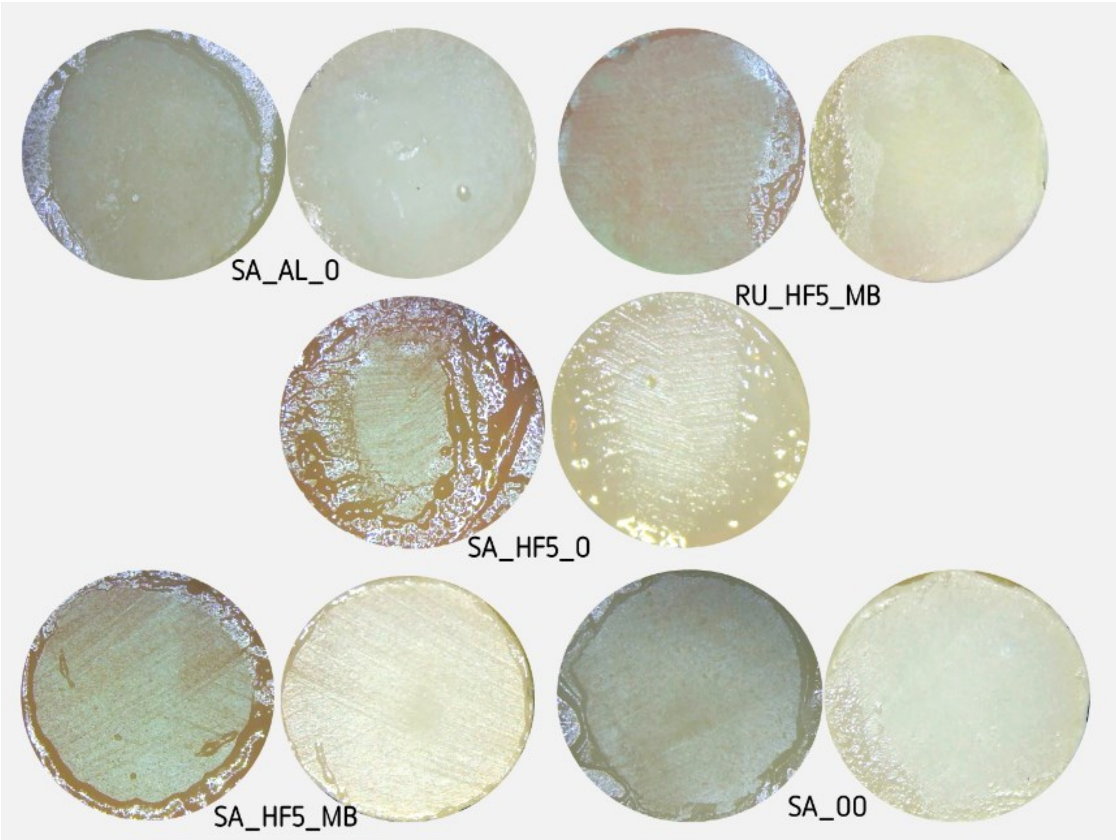

Figure 30 – Microscopic observation of the adhesive joint interface surfaces (50x ampliation) displayed by the cementation protocol showing the characteristic mode of fracture for each protocol (left, FRASACO tooth) (right, cement cylinder)

The adhesive strength was affected by the surface treatment and the use of Monobond Plus as the coupling agent. For the Panavia SA cement in self-curing mode, the best surface treatment of the adherend FRASACO tooth was aluminum oxide blasting. No difference existed between no additional treatment or coupling agent application and the adhesion to only grinded tooth.

Relative to the fracture mode (Fig. 30), all adhesive protocols except SA_HF5_0 were associated with adhesive failure in almost all interfaces, with peripheric cohesive failure of

the cement. In the case of SA_HF5_0, the mode of failure was mixed (adhesive and cohesive). No cohesive failure occurred in the FRASACO teeth.

Relevance: Despite the low values obtained with this experimental setting, it was possible to segregate adhesive protocols by surface treatment and coupling agent, demonstrating a marked dependence of the adhesive cement on the procedure, a fact that should alert clinicians to the need to know the materials available in-depth and not to associate components with each other without foundation. Similar protocols or products may lead to very different adhesive efficiencies.

3.5 Testing a new RBB specimen model (Task 3)

A new experimental model was used to test new experimental conditions, incorporating data from previous tasks. This task aimed to validate the model, but also to evaluate the comparative shear bond strength of the Panavia SA self-etch adhesive cement and that of a universal adhesive, the Scotchbond Universal, for eventual transposition of the experimental protocols to task 5. The best-performing combination obtained in previous tasks, Rely X Ultimate (adhesive cement) coupled with Monobond Plus (coupling agent) in the ENA setting, was used as the positive performance reference and Panavia SA (adhesive cement) in the self-etch mode without the coupling agent associated in the ENA setting was the negative performance reference for the assessment. This model was conceived to reduce bending and to allow for a distance between the bases more similar to the distance of an absent tooth due to MLIA. The main materials used are shown in Table 8, and in Figure 31 a graphical representation of the mechanical test is shown.

Table 8 – Main materials used to test a new RBB specimen model

Material	Name	Code	Composition	Manufacturer
CAD-CAM Monolithic ceramics	VITA Enamic	ENA	86% feldspar ceramic: SiO_2 58–63%, Al_2O_3 20–23%, Na_2O 9–11%, K_2O 4–6% by weight, 14% polymer by weight: TEGDMA, UDMA	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA Suprinity	SUP	Zirconium oxide 8–12, silicon dioxide 56–64%, lithium oxide 15–21%, various > 10% by weight	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA 5Y-TPZ Color	Y-ZPT	Zirconia reinforced with 5% Yitria	VITA Zahnfabrik, Bad Säckingen, Germany
Resin-matrix composite cement	RelyX Ultimate	RU	MDP phosphate monomer, dimethacrylate resins, HEMA, Vitrebond™ copolymer filler, ethanol, water, initiators, silane	3M Oral Care, St. Paul, MN, USA
Etching agent	Porcelain Etch Gel	PEG	Hydrofluoric acid 9.6%	Pulpdent, Watertown, MA, USA
Ceramic primer	Monobond Plus	MB	50–100% ethanol, disulfit methacrylate, ≤2.5% phosphoric acid dimethacrylate, ≤2.5% 3-trimethoxysilylpropyl methacrylate	Ivoclar Vivadent AG, Schaan, Liechtenstein
Adhesive system	Scotchbond Universal adhesive	SBU	MDP, Bis-GMA, phosphate monomer, dimethacrylate resins, HEMA, methacrylate-modified polyalkenoic acid copolymer, filler, ethanol, water, initiators, silane-treated silica	3M Oral Care, St. Paul, MN, USA

Bis-GMA, bisphenol A glycidyl methacrylate; HEMA, 2-hydroxyethyl methacrylate; MDP, 10-methacryloyloxydecyl dihydrogen phosphate; TEGDMA, triethylene glycol dimethacrylate; UDMA, urethane dimethacrylate

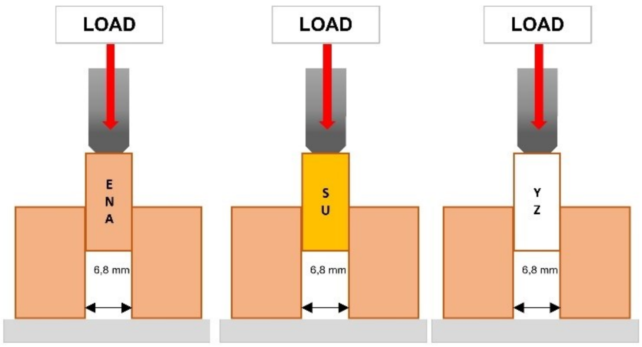

Figure 31 – Graphical representation of the experimental protocol of shear bond test

The experimental groups are shown in Table 9. The components of the specimen were prepared following the same procedures described in Papers 5 and 6 for each type of material, and some details are shown in Figures 32 to 35.

Table 9 - Experimental groups by type of material, surface treatment, and coupling agent used

CEMENT	CAD-CAM Bar	SURFACE TREATMENT Base	SURFACE TREATMENT Bar	COUPLING AGENT
Panavia SA (SA_00_ENA)	ENAMIC	Grinding	5% HF 60 s	None
Panavia SA (SA_00_YZ)	ZIRCONIA	Grinding	Al_2O_3 blasting	None
Rely X Ultimate (RU_MB_ENA)	ENAMIC	5% HF 60 s	5% HF 60 s	Monobond Plus
Rely X Ultimate (RU_MB_SU)	SUPRINITY	5% HF 60 s	5% HF 20 s	Monobond Plus
Rely X Ultimate (RU_MB_YZ)	ZIRCONIA	5% HF 60 s	Al_2O_3 blasting	Monobond Plus
Rely X Ultimate (RU_SBU_ENA)	ENAMIC	5% HF 60 s	5% HF 60 s	Scotchbond Universal
Rely X Ultimate (RU_SBU_SU)	SUPRINITY	5% HF 60 s	5% HF 20 s	Scotchbond Universal
Rely X Ultimate (RU_SBU_YZ)	ZIRCONIA	5% HF 60 s	Al_2O_3 blasting	Scotchbond Universal

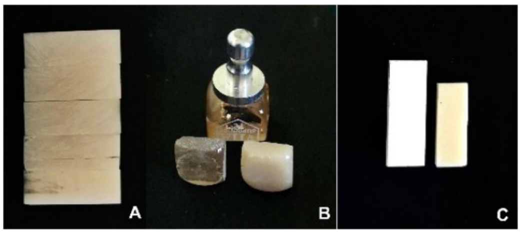

Figure 32 - Specificities of bar manufacturing. (A) Enamic bars immediately after cutting with a circular diamond saw, without need for further processing; (B) Suprinity before (left) and after crystallization in the furnace; and (C) Y-ZPT bar immediately after cutting (left) and after furnace sinterization, with evident size reduction, implying an initial 1.24% oversize.

The assembly of the specimen components was standardized using adhesive tape to prevent the leakage of the adhesive beyond the desired area, and also by the use of a polyurethane foam bar to support the settlement of the bar during polymerization.

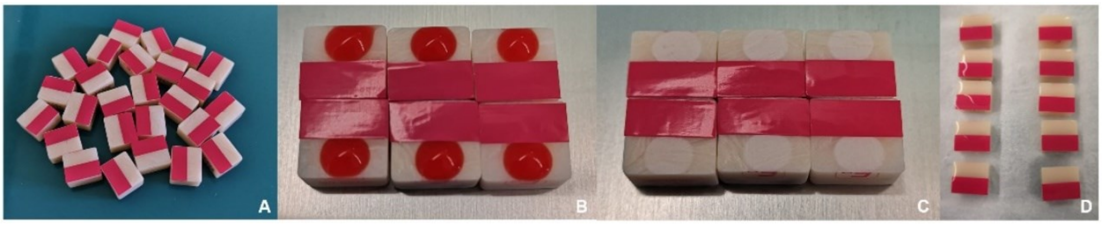

Figure 33 – Preparation of the bases for the specimens. (A) Randomization; (B) Surface treatment with 5% hydrofluoric acid, 60 s; (C) after washed with oil-free air-water spray for 30 s; (D) during the drying of the coupling agent, 60 s, and after another randomization

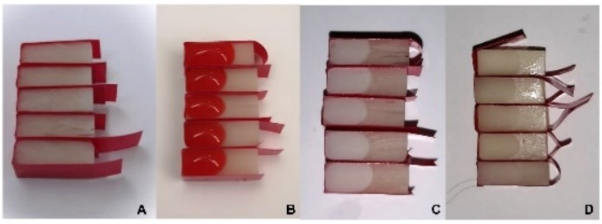

Figure 34 – Vita Enamic bars during surface treatment. (A) with the lateral sides protected by adhesive tape to restrain the treated area; (B) 5% hydrofluoric acid, 60 s; (C) after washed with oil-free air-water spray for 30 s; (D) during drying of the coupling agent, 60 s

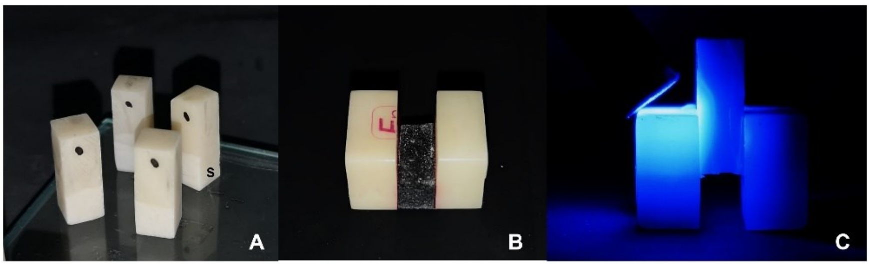

Figure 35 - Procedures for assembling specimens. (A) three Enamic bars and one Suprinity bar (s) waiting assemblage; (B) bases positioned for assembling with the interposition of the polyurethane foam bar; (C) detail of the polymerization step (20 s on each side, total 80 s), highlighting the translucency of the base material.

The assembled specimens and a detail of a specimen positioned for the shear bond test are shown in Figure 36.

Figure 36 - Specimens prepared for the shear bond test, according to the adhesive cement, surface treatment of the base and bar and coupling agent used, together with a detail of the loading procedure

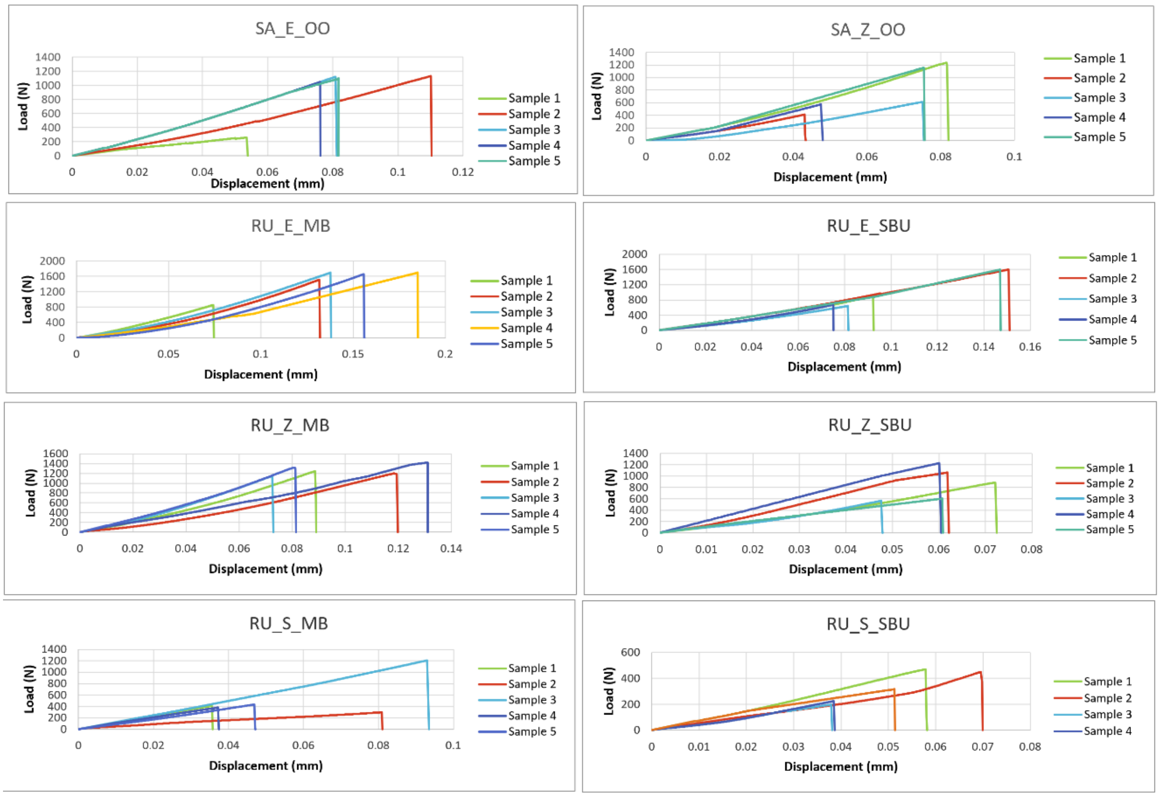

Figure 37 - Graphic representation of specimen behavior under load. The SA_E_OO group was the negative and the RU_E_MB group was the positive reference

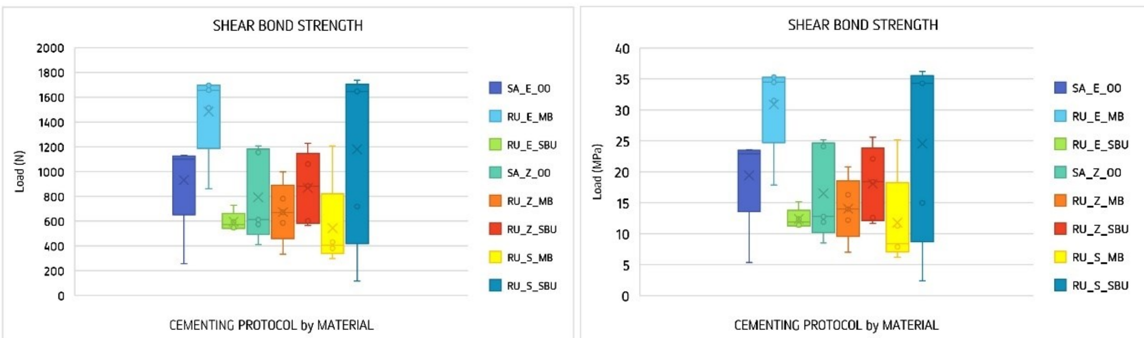

Figure 38 - Box plot of load to fracture (N) and adhesive strength (MPa) by CAD-CAM ceramics and adhesive protocol (RU_E_MB, positive reference; SA_E_OO, negative reference)

Table 10 - Mean ± standard deviation of load to fracture (N) and adhesive strength (MPA) by group

CAD-CAM MATERIAL	ADHESIVE CEMENT	COUPLING AGENT	SAMPLE	LOAD	STRENGTH
VITA ENAMIC	Panavia SA	None	1	256.9	5.4
			2	1131.3	23.6
			3	1120.9	23.4
			4	1046.4	21.8
			5	1099.8	22.9
			MEAN	**931.0**	**19.4**
			MEDIAN	**1099.8**	**22.9**
			SD	**378.3**	**7.9**
	Rely X Ultimate	Monobond Plus	1	860.6	17.9
			2	1513.5	31.5
			3	1696.7	35.3
			4	1695.8	35.3
			5	1657.4	34.5
			MEAN	**1484.8**	**30.9**
			MEDIAN	**1657.4**	**34.5**
			SD	**356.9**	**7.4**
	Rely X Ultimate	Scotchbond Universal Adhesive	1	594.4	12.4
			2	571.0	11.9
			3	547.6	11.4
			4	728.0	15.2
			5	535.4	11.2
			MEAN	**595.3**	**12.4**
			MEDIAN	**571.0**	**11.9**
			SD	**77.5**	**1.6**
VITA Y-ZPT	Panavia SA	None	1	1156.1	24.1
			2	573.5	11.9
			3	612.3	12.8
			4	410.2	8.5
			5	1209.0	25.2
			MEAN	**792.2**	**16.5**
			MEDIAN	**612.3**	**12.8**
			SD	**364.8**	**7.6**
	Rely X Ultimate	Monobond Plus	1	996.8	20.8
			2	586.0	12.2
			3	781.4	16.3
			4	670.3	14.0
			5	335.0	7.0
			MEAN	**673.9**	**14.0**
			MEDIAN	**670.3**	**14.0**
			SD	**244.1**	**5.1**
	Rely X Ultimate	Scotchbond Universal Adhesive	1	883.5	18.4
			2	1061.4	22.1
			3	564.0	11.7
			4	1229.0	25.6
			5	602.6	12.6
			MEAN	**868.1**	**18.1**
			MEDIAN	**883.5**	**18.4**
			SD	**287.6**	**6.0**
VITA SUPRINITY	Rely X Ultimate	Monobond Plus	1	404.9	8.4
			2	298.0	6.2
			3	1207.6	25.2
			4	381.1	7.9
			5	431.4	9.0
			MEAN	**544.6**	**10.3**
			MEDIAN	**404.9**	**8.4**
			SD	**374.0**	**7.8**
	Rely X Ultimate	Scotchbond Universal Adhesive	1	117.2	2.4
			2	1738.3	36.2
			3	718.2	15.0
			4	1647.2	34.3
			5	1673.6	34.9
			MEAN	**1178.9**	**24.6**
			MEDIAN	**1647.2**	**34.3**
			SD	**727.4**	**15.2**

From the observation of Figures 37 and 33, and Table 10, we can say that the results validated the model, as it allowed us to detect marked differences in the mechanical behavior of the adhesive joint according to the material, the coupling agent, and the adhesive cement used. Furthermore, the supported load reached interesting values for clinical application. To calculate the adhesive strength, an adhesive interface of A_{base} = 4.8× 5x 2= 48 mm^2, was considered.

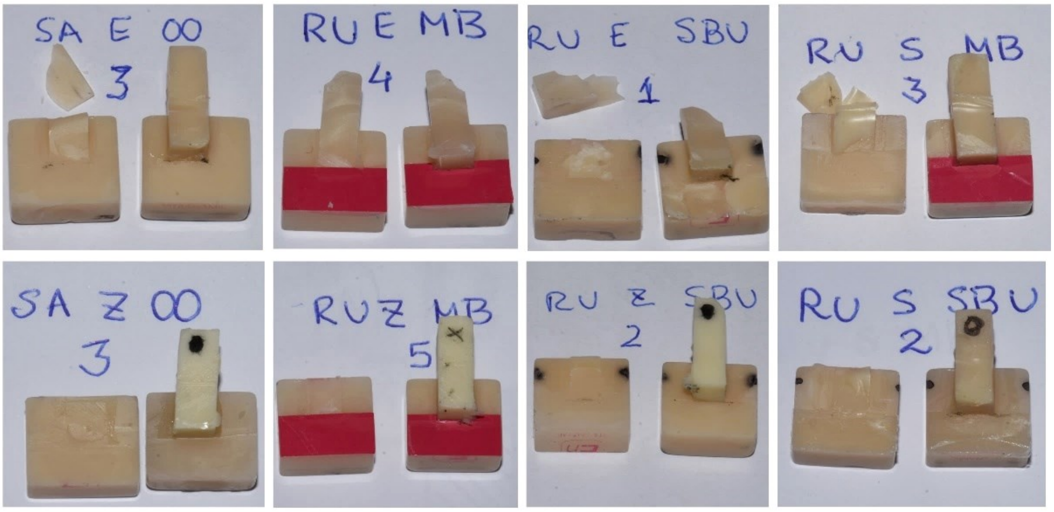

Figure 39 - Representative mode of failure according to group (E, Enamic; S, Suprinity; RU, Rely X Ultimate; SA, Panavia; MB, Monobond Plus, SBU, Scotchbond Universal adhesive; 00, only grinding as surface treatment.

As shown in Figure 39, the failure mode was adhesive for Y-ZPT, and cohesive in the bar for ENA and SU. Suprinity, despite being an interesting material in terms of esthetic, finishing, and polishing results, is a difficult material to work with, as it is very brittle during the cut. This fact also conditioned, in our opinion, the mechanical results because, whenever subjected to load, the test bar failed due to catastrophic fracture (cohesive failure of the bar and not adhesive failure of the joint) probably due to fine irregularities caused by the cutting step.

To better understand the tested materials, the compression strain of the CAD-CAM ceramics was assessed. In Figure 40 the main differences are evident. The Y-ZPT test was aborted around 1225 MPa of compressive stress under a load of 75.000 N, and the mean ± standard deviation values for Vita Enamic and Vita Suprinity were, respectively, 294.40 ± 66.2 and 522.40 ± 274.00 MPa.

Suprinity specimens showed significant variation in the strength and stiffness and this could be related to the difficult handling. This fact is probably due to some irregularity of the borders and on the top, conducting a compression test more concentrated in a portion of the top area, which could influence individual performance. The mechanical behavior of Enamic specimens show similar stiffness and similar strength was more constant than the Suprinity specimens. Due to simplicity in handling was possible to obtain specimens with the same geometry showing similar mechanical compressive behavior, three specimens show a progressive failure mechanism due to moderate plasticity. Due to the high stiffness of Y-ZPT, was not possible to break the specimens. The strength reached (> 1225 MPa) was enough to deform plastically the steel used to test the specimens. In Figure 41 the toughness of Y-ZPT can be proven by observation of the imprint on the high-strength steel support done by the specimen during the test.

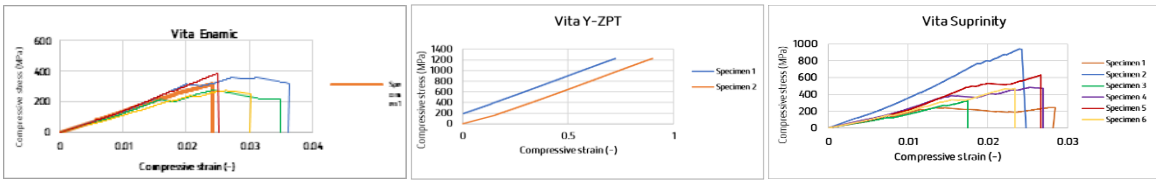

Figure 40 - Graphical representation of the compressive strain of the CAD-CAM ceramics used in this task.

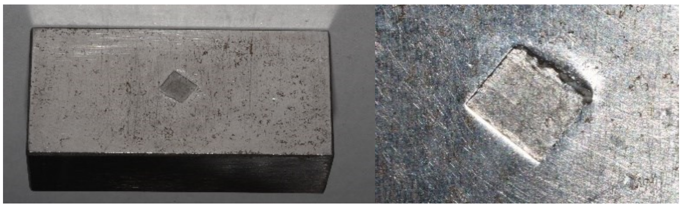

Figure 41 - Pressure mark on the tempered steel support made by the Y-ZPT cube during the compression strain test

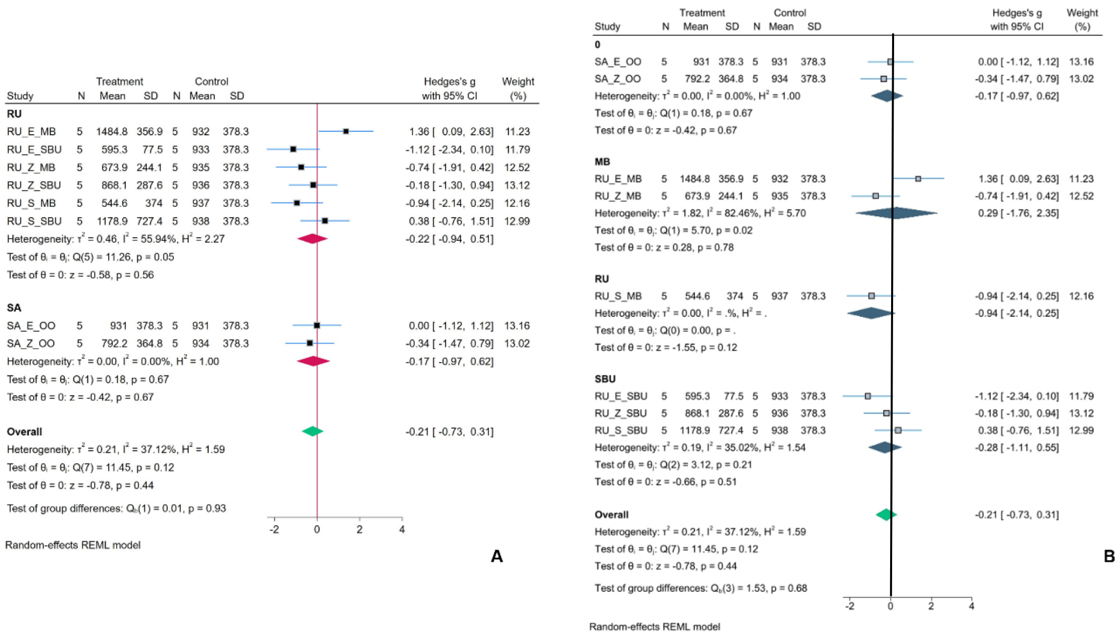

Figure 42 - Forest plots comparing the effect size after calculation of the difference in means of the shear bond strength between adhesive protocols, by protocol and by coupling agent

Concerning the adhesive protocol, the comparison of groups (Fig. 42 A) revealed that, except for the RU_S_SBU group, none of the others reached values similar to the positive reference. On the other hand, the adhesive combination chosen for negative reference did not behave less than the other groups and was even superior to the combination RU_E_SBU. When it comes to the coupling agent, the Monobond Plus (MB) proved to be the most effective for Vita Enamic and the Scotchbond Universal for Suprinity.

Concerning PANAVIA SA cement, its adhesive performance was very similar to that of Rely X Ultimate (RU) for zirconia. It should be noted that this cement was used in self-etch mode, that is, without surface treatment or coupling agent.

From the observation of Figure 42 A, only the difference between positive and negative references is significant ($\alpha=0.05$; $p<0.05$), and the effect of the material (Enamic or Y-ZPT) on the shear strength of the same adhesive protocol ($\alpha=0.05$; $p<0.05$).

In conclusion, the new experimental model allowed a comparative evaluation of the shear bond strength of the self-etching adhesive cement Panavia SA and that of a 3-step dual-cured adhesive cement, Rely X Ultimate, for eventual transposition of the experimental protocols to task 5. The results validated the proposed model and revealed marked differences in the mechanical behavior of the adhesive joint according to the material, the coupling agent, and the adhesive cement used. Furthermore, the supported load was interesting for clinical application. The Monobond Plus was the more effective coupling agent for Enamic and the Scotchbond Universal for Suprinity. The PANAVIA SA was similar to the Rely X Ultimate for zirconia.

Clinical Relevance: The RU had better performance associated with MB to adhere to Enamic and with SBU to adhere to Suprinity. To adhere to zirconia, any of the options is feasible. The less tough material (Vita Enamic) was the one that performed better. The Vita Suprinity revealed brittleness and Vita Y-ZPT adhesive weakness.

3.6 Evaluation of the shear strength of natural teeth and comparison with artificial adherends (Task 4)

The tests developed in the previous tasks may make more sense compared to similar mechanical tests in natural teeth. For this, we used extracted human teeth (central incisors, n=20), voluntarily donated by the patients after having succinctly explained the purpose of the study to them. No request was made to the Ethics Committee because these teeth, if not used in this study, would have been discarded in biological waste, and under no condition was the extraction of the teeth conditioned by the interest of the research. The collected teeth were cleaned and immediately kept at a temperature between 2-8°C, after immersion in an appropriate conservation medium (Hank's balanced salt solution, Merck KGaA, Darmstadt, Germany). No teeth stored for more than 6 months were used. Table 11 presents the main materials for this task.

Table 11 - Materials used in the study

Material	Name	Code	Composition	Manufacturer	Batch No.
CAD-CAM Ceramics	VITA Enamic	ENA	86% feldspar ceramic: SiO_2 58–63%, Al_2O_3 20–23%, Na_2O_9–11%, K_2O_4–6% by weight, 14% polymer by weight: TEGDMA, UDMA	VITA Zahnfabrik, Bad Säckingen, Germany	74770
Artificial teeth	FRASACO	FRA	Melamine-based composition	Frasaco GmbH, Tettnang, Germany	A3 E 110
Natural teeth	N/A	NT	Natural enamel and dentin	n/a	n/a
Resin Composite Cement	Panavia SA Cement Universal	SA	Paste A: MDP, Bis-GMA, TEGDMA, HEMA, silanated barium glass filler, silanated colloidal silica, dl-camphorquinone, peroxide, catalysts, pigments Paste B: HEMA, silane, silanated barium glass filler, aluminum oxide filler, sodium fluoride (<1%), dl-camphorquinone, accelerators, pigments	Kuraray Europe GmbH, Hattersheim, Germany	4N0174 Exp. 2025-02-28
	RelyX Ultimate	RU	MDP phosphate monomer, dimethacrylate resins, HEMA, Vitrebond™ copolymer filler, ethanol, water, initiators, silane	3M, St. Paul, MN, USA	9592748 Exp. 2024-06-12
Etching agent	VITA ADIVA Cera Etch	HF	Hydrofluoric acid 5%	VITA Zahnfabrik, Bad Säckingen, Germany	94450 Exp. 2024-09-30
	Scotchbond Universal Etchant	PA	Phosphoric acid 35%	3M ESPE, Minneapolis, MN, USA	9513787 Exp. 2024-11-16
Ceramic primer and Adhesive system	Monobond Plus	MB	50–100% ethanol, disulfit methacrylate, ≤2.5% phosphoric acid dimethacrylate, ≤2.5% 3-trimethoxysilylpropyl methacrylate	Ivoclar Vivadent AG, Schaan, Liechtenstein	Z01XT0 Exp. 2023-03-24
	Scotchbond Universal adhesive	SB-U	MDP, Bis-GMA, phosphate monomer, dimethacrylate resins, HEMA, methacrylate-modified polyalkenoic acid copolymer, filler, ethanol, water, initiators, silane-treated silica	3M Oral Care, St. Paul, MN, USA	Scotchbond Universal adhesive

Information on the composition of the materials was obtained from the manufacturers' websites and SDS documents. Bis-GMA, Bisphenol A-diglycidylmethacrylate; HEMA, 2-hydroxymethacrylate; MDP, 10-methacryloyloxydecyl dihydrogen phosphate; TEGDMA, triethyleneglycol dimethacrylate; UDMA, diurethane dimethacrylate.

Since this task aimed to compare the shear strength of adhesive cements adhered to the natural tooth with the shear strength of these same adhesives adhered to artificial substrates (Vita Enamic block and Frasaco Teeth) to complement the results obtained with the natural tooth, some values obtained in tasks 2.2 and 2.3 were used. Since selected Vita Adiva IA-CEM cement (VITA Zahnfabrik, Bad Säckingen, Germany) is not advisable in the anterior sector of the maxilla due to opacity,[37] it was not tested in this task.

Details of surface treatment, polymerization, and cylinder build-up are shown in Figures 43 to 45, and standardization with those from tasks 2.2 and 2.3 was guaranteed.

The settings for the shear bond test were similar to those reported in **Paper 6**, but specific details can be observed in Table 12 and Figure 46.

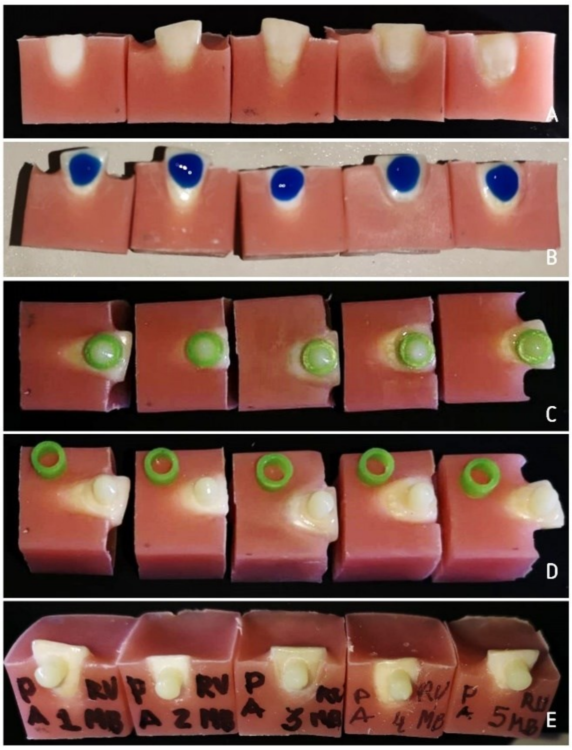

Figure 43 - Steps of the fabrication of five specimens of the group RU_PA_MB (A) teeth embedded in acrylic resin, ready for surface treatment; (B) conditioning with of phosphoric acid 30s; (C) cement cylinder building, with the help of calibrated silicon mold; silicon mold removal; (D) specimens after identification

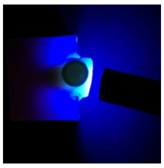

Figure 44 - Photopolymerization step showing incident light through the buccal surface of the tooth during the initial 20s of a total of 60 s (additional 20 s from mesial and 20 s from distal).

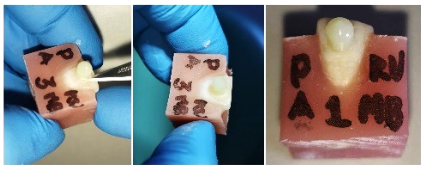

Figure 45 - Removal of excess cement, to limit the area of the interface joint to the area of the cylinder

Table 12 – Luting cements, subgroups, surface treatments, and coupling agents used in this study

Group	Substrate	Cement	Surface Treatment	Coupling Agent
SA_00	ENAMIC	Panavia SA	Grinding	None
SA_HF5_MB	ENAMIC	Panavia SA	5% Hydrofluoric acid	Monobond Plus
RU_HF5_MB	ENAMIC	Rely X Ultimate	5% Hydrofluoric acid	Monobond Plus
SA_00	FRASACO	Panavia SA	Grinding	None
SA_AL_0	FRASACO	Panavia SA	Al_2O_3 blasting	None
SA_HF5_0	FRASACO	Panavia SA	5% Hydrofluoric acid	None
SA_HF5_MB	FRASACO	Panavia SA	5% Hydrofluoric acid	Monobond Plus
RU_HF5_MB	FRASACO	Rely X Ultimate	5% Hydrofluoric acid	Monobond Plus
SA_PA_MB	NATURAL TOOTH	Panavia SA	35% Phosphoric acid	Monobond Plus
RU_PA_MB	NATURAL TOOTH	Rely X Ultimate	35% Phosphoric acid	Monobond Plus

Figure 46 - Schematic representation of the mechanical test and two details of the testing. (A) stationary base; (B) specimen with the natural tooth embedded in acrylic resin; (C) fixing device; (D) loading cell and piston; (E) cement cylinder adhered to the tooth

All base surfaces (teeth) were initially ground. The adherend Enamic adhered to a cylinder made of Panavia SA with no coupling agent was the control group. For the other groups, the surface treatment was only grinding, 5% hydrofluoric acid, or Al_2O_3 blasting according to the material and adhesive protocol, as can be seen in Table 13, along with the coupling agent used. Table 13 compiles the mean and standard deviation of the results used for comparison, which are graphically represented in Figure 47 for a more intuitive understanding.

Table 13 - Mean ± standard deviation (SD) by cementing protocol, in Newtons (N) and megapascals (MPa)

CEMENT	SUBSTRATE	SHEAR STRENGTH	
		Mean ± SD (N)	Mean± SD (MPa)
Panavia SA (SA_00)	ENAMIC	119.97 ± 43.05	19.09 ± 6.85
Panavia SA (SA_HF5_MB)	ENAMIC	180.59 ± 20.27	28.74 ± 3.23
Rely X Ultimate (RU_HF5_MB)	ENAMIC	349.12 ± 26.94	55.56 ± 4.29
Panavia SA (SA_00)	FRASACO	26.66 ± 9.12	4.24 ± 1.45
Panavia SA (SA_0_AL)	FRASACO	58.36 ± 9.95	9.29 ± 1.58
Panavia SA (SA_HF5_0)	FRASACO	35.73 ± 24.30	5.69 ± 3.87
Panavia SA (SA_HF5_MB)	FRASACO	28.59 ± 12.61	4.55 ± 2.01
Rely X Ultimate (RU_HF5_MB)	FRASACO	65.33 ± 15.23	10.40 ± 2.42
Panavia SA (SA_PA_MB)	TOOTH	88.5 ± 40.6	14.09 ± 6.46
Rely X Ultimate (RU_PA_MB)	TOOTH	115.19 ± 31.98	18.33 ± 5.09

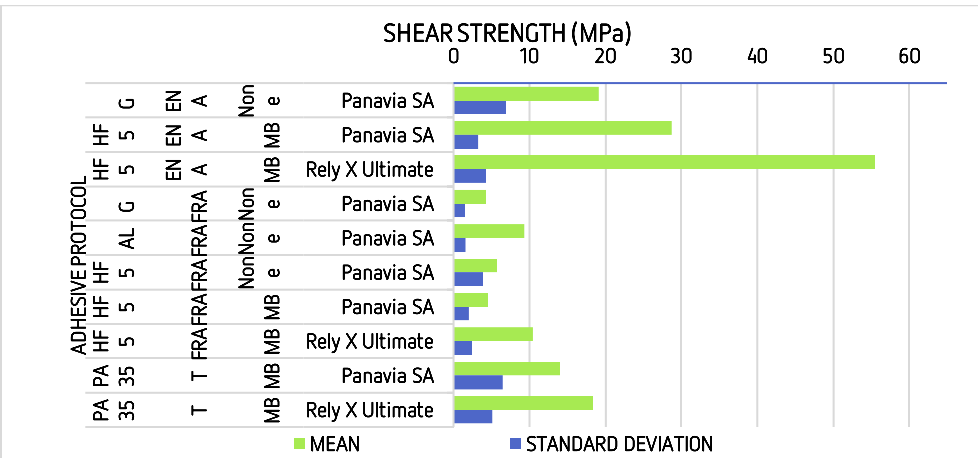

Figure 47 - Shear bond strength of different adhesive protocols according to different adherent bases (Enamic, FRASACO tooth, and natural tooth). AL, aluminum oxide; ENA, Enamic; FRA, Frasaco tooth; G, grinding; HF, hydrofluoric acid; PA, phosphoric acid; T, natural tooth

In Figures 48 to 50 the effect of the surface treatment on each material (Enamic, Frasaco tooth, or natural enamel) is shown under a 50x ampliation. Table 14 shows the results of the surface energy measurement performed according to the methodology described in **Paper 6**.

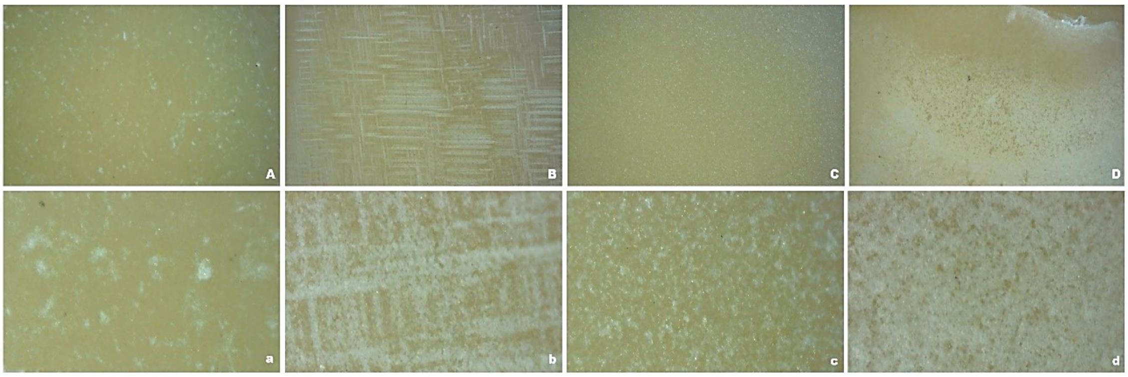

Figure 48 - Enamic block under different surface treatments (50x ampliation - capital letters; 100x ampliation- small letters). (A, a) surface as provided by the manufacturer; (B, b) surface grinded by coarse diamond bur (C, c); surface after 50µm aluminum oxide blasting (D, d), and surface after 5% hydrofluoric acid for 60 s.

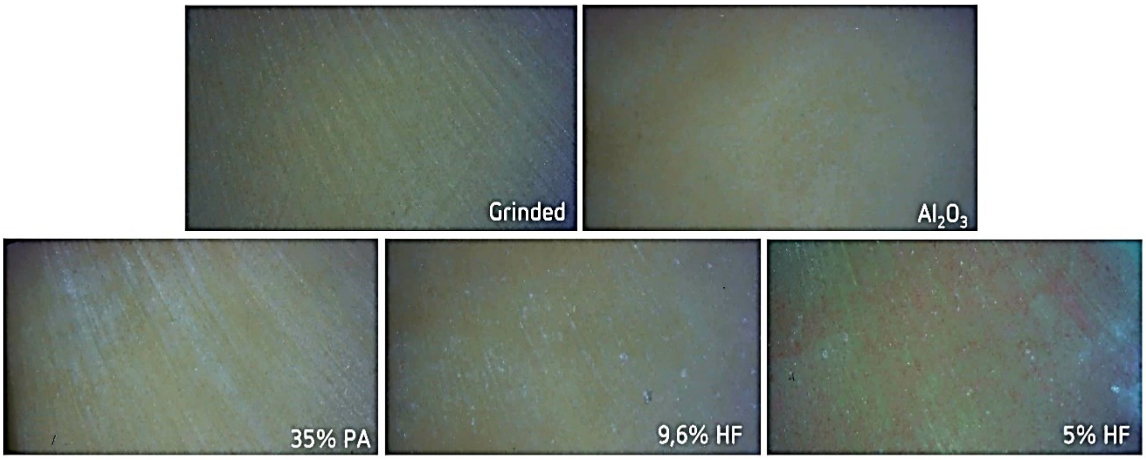

Figure 49 – Frasaco tooth just grinded and after different surface treatments (50x ampliation)

Figure 50 - Different surface treatments of natural enamel (50x ampliation). Surface treatment by grinding with a coarse diamond bur (A), aluminum oxide blasting (B), and 35% phosphoric acid for 30 s

Table 14 - Block surface energy, determined by measurement of contact angle

	SURFACE ENERGY (mJ/m²)				
	Grinding	Sandblasting	35% PA	5% HF	9.6% HF
VITA Enamic	37.2	**46.9**	n/a	37.2	n/a
FRASACO	51.41	56	58.81	**68.55**	67.73
TOOTH	56.82	60.98	**63.73**	n/a	n/a

The comparative evaluation of the surface energy revealed that of all substrates, the one with the worst surface energy characteristics was Vita Enamic. Relatively, the differences observed between the FRASACO tooth and the natural tooth were not significant. However, when we cross these data with mechanical results, we are forced to admit that surface energy was not a preponderant factor in the final result, because Enamic as adherend was the one that obtained the best performance. It is then legitimate to say that chemical phenomena contributed to this mechanical performance of the hybrid ceramic Vita Enamic.

Following off-record direct information from the manufacturer, the FRASACO tooth is based on melamine, which theoretically exhibits limited reactivity because of its stable chemical structure. It is sensitive to strong acids and may undergo hydrolysis reaction with breaks in the triazine ring, and substitution of one or more amino groups in melamine with alkyl groups.

Alkylated melamine compounds may possess different properties or functionalities compared to those of melamine itself, depending on the nature of the alkyl groups introduced. Again, chemical issues must be involved to justify differences in the results of shear bond strength with different adhesive cement but with the same surface treatment and coupling agent (SA_HF5_MB, 4.55 ± 2.01 MPa; RU_HF5_MB, 10.40 ± 2.42 MPa).

Relevance: Any of the artificial substrates can be considered reliable substitutes for shear strength tests under experimental conditions similar to those used.

3.7 Testing a simulated RBB for MLIA rehabilitation (Task 5) (Paper 7)

This task was developed to test the bond strength of RBBs produced from four CAD-CAM materials (3 monolithic ceramics and a 3D-printed polymer) adhered to an artificial tooth, simulating a real clinical case. Detailed steps of the experimental protocol are accessible in **Paper 7.**

The artificial maxilla was assessed as in the case of a real mouth. The intraoral scanner captured the images (Fig. 51) to be processed with the appropriate software used in dental laboratory procedures.

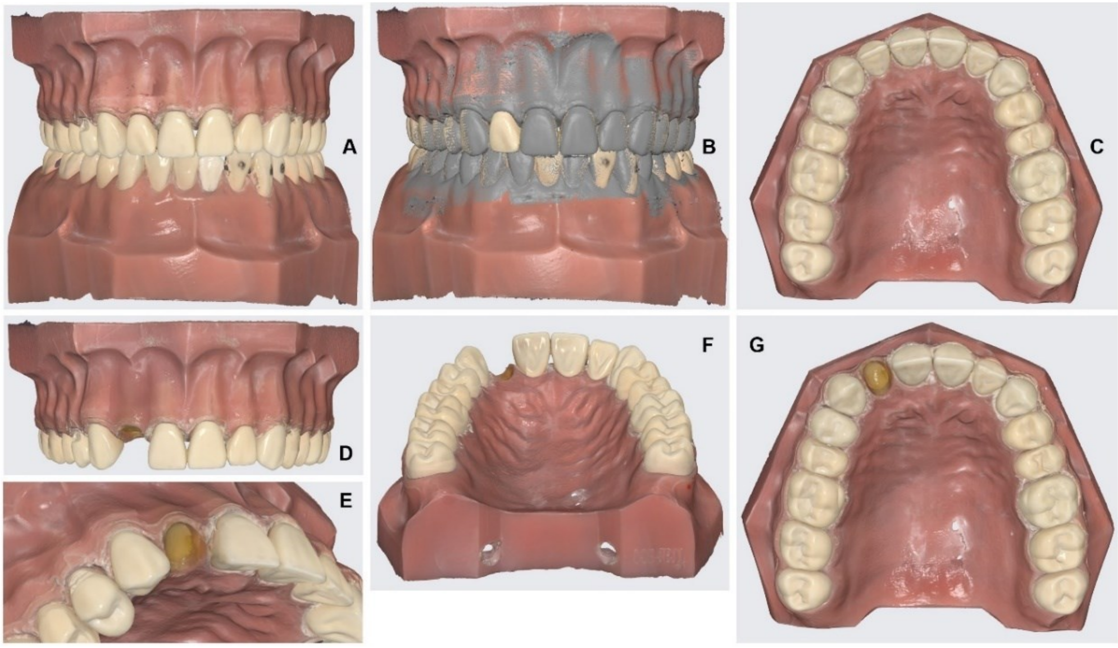

Figure 51 - Images acquired by intraoral scanner. (A) reference data from both maxillaries in front view, (B) occlusion data, (C) reference maxilla in occlusal view, (D) maxilla simulating a lateral incisor agenesis, (E) the same in detail, (F) view from palatal; (G) maxilla simulating a lateral incisor agenesis in occlusal view

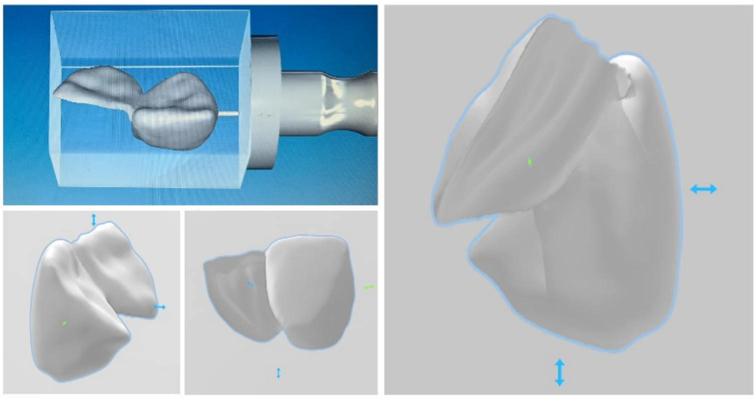

Figure 52 - Details of the RBBs design

A single-retainer resin-bonded bridge (Fig. 52), was designed under manufacturing protocols the same as for a real clinical situation of MLIA rehabilitation. The materials and cementing protocols are detailed in Table 15.

Table 15 - Materials used for adherend surface treatment and adhesion

CEMENT	SUBSTRATE	SURFACE TREATMENT (Frasaco Tooth)	SURFACE TREATMENT (RBB)	ADHESIVE SYSTEM
Rely X Ultimate	ABS	5% Hydrofluoric acid	Heliobond	Scotchbond Universal
	ENAMIC	5% Hydrofluoric acid	9.6% Hydrofluoric acid 60 s	
	SUPRINITY	5% Hydrofluoric acid	9.6% Hydrofluoric acid 20 s	
	Y-ZPT	5% Hydrofluoric acid	Al_2O_3 sandblasting	

Figure 53 (A and B) shows the sintered Y-ZPT RBBs before and after surface treatment with 50 µm aluminum oxide set at 0.25 MPa, for 10 s, 1 mm, with erratic movements. Figures 54 to 56 show more information about the procedures.

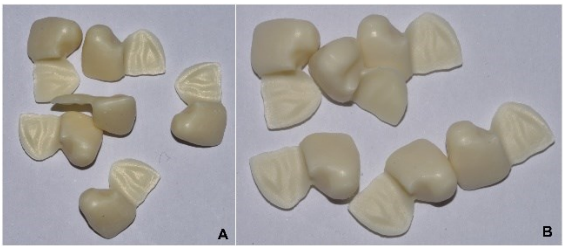

Figure 53 - Adhesion surface of RBB Y-ZPT (A) before and (B) after surface treatment with Al_2O_3 sandblasting with loss of the slight glossy surface generated by milling

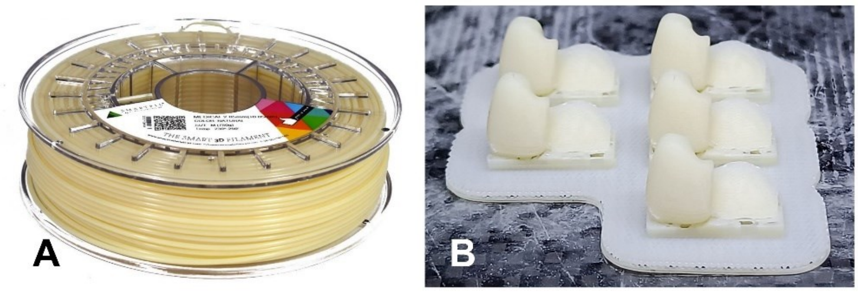

Figure 54 - ABS spool with filament, (A) and (B) RBBs immediately after fusion printing, ready for manual finishing.

Figure 55 - Example of ENA, SUP, and ABS RBBs ready for the SBS test.

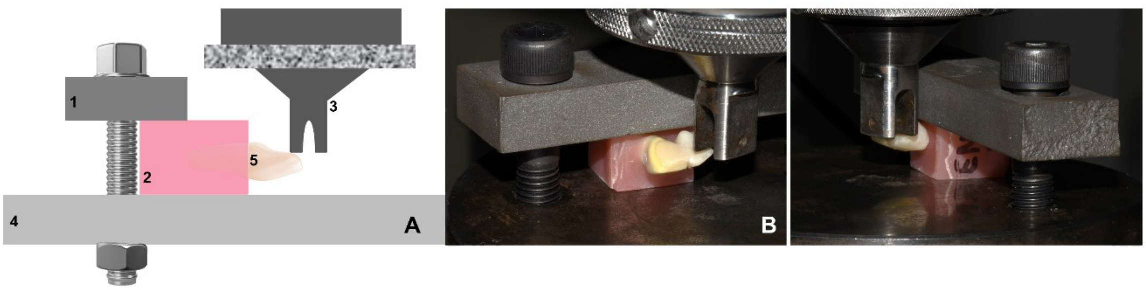

Figure 56 – Graphical representation and photographs of the shear bonding test (A) Components designed for testing (1, block stabilizer; 2, adherend base incorporated in acrylic resin block; 3, load cell and piston; 4, stationary base; 5, RBB to be tested); (B) block stabilized on stationary base and RBB tooth positioned for SBS; (C) piston positioned, over the cylinder, 2 mm away from the incisal border.

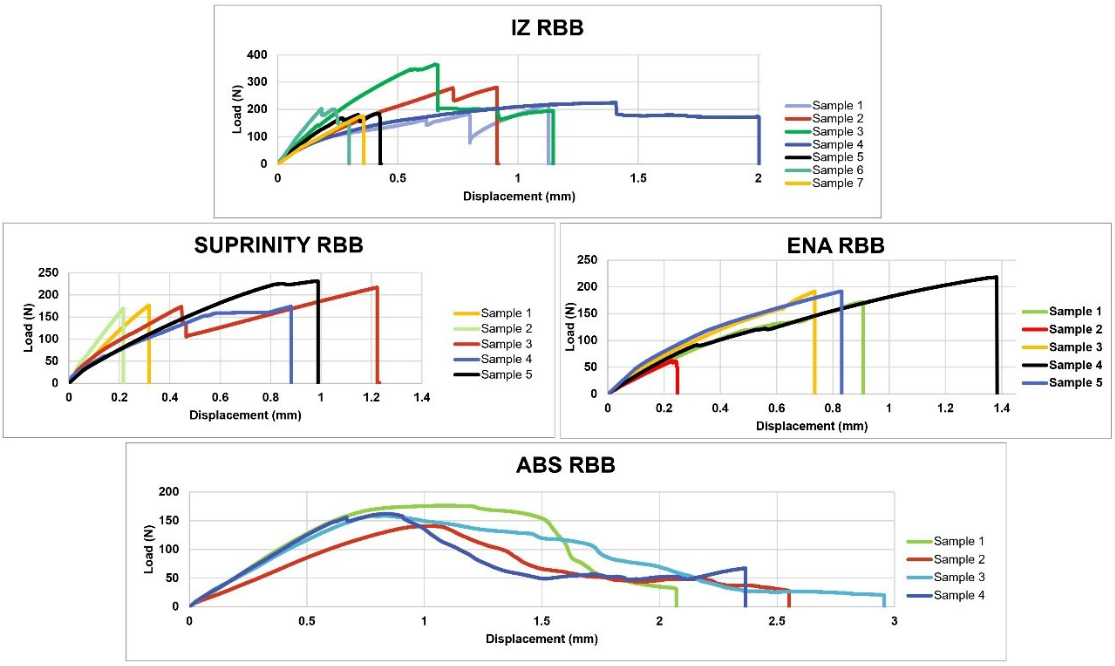

Figure 57 - Behavior of samples under load, from control group (Y-ZPT), Suprinity, Enamic, and ABS groups

Although it was known, based on the results of the previous tasks, that the shear strength of the FRASACO teeth would not be very high, their resistance was sufficient to evidence the different behavior of the RBBs, since exclusive adhesive failure was verified only for RBBs manufactured with zirconia, a material with high toughness. On the other hand, these teeth have a standardized composition and anatomy, allowing to eliminate the bias originated by biological factors or different macroanatomies of the incisor lingual face, which

could happen if natural teeth have been used, with only slight asperization intended, as in a minimally invasive approach.

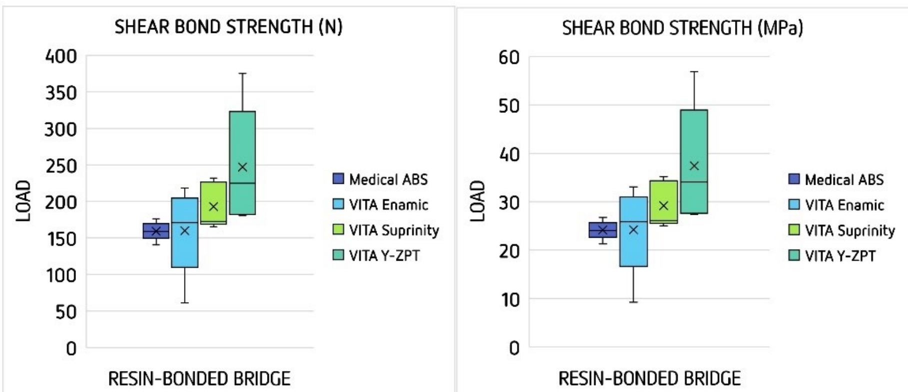

Figure 58 - Box plots of the RBB shear strength by material type in absolute load to fracture (N) and relative load to fracture (MPa)

The SBS test (Figs. 57 and 58) showed that Y-ZPT RBBs had the highest bond strength of all tested materials. The compared mean ± standard deviation SBS values found were ENA (24.24 ± 9.05 MPa) < ABS (24.01 ± 1.94 MPa) < SUP (29.17 ± 4.78 MPa) < Y-ZPT (37.43 ± 12.20 MPa). The failure modes were mainly adhesive for Y-ZPT, cohesive for SUP and ENA, and cohesive with plastic deformation for ABS. Failure modes can be observed in Figures 59 and 60.

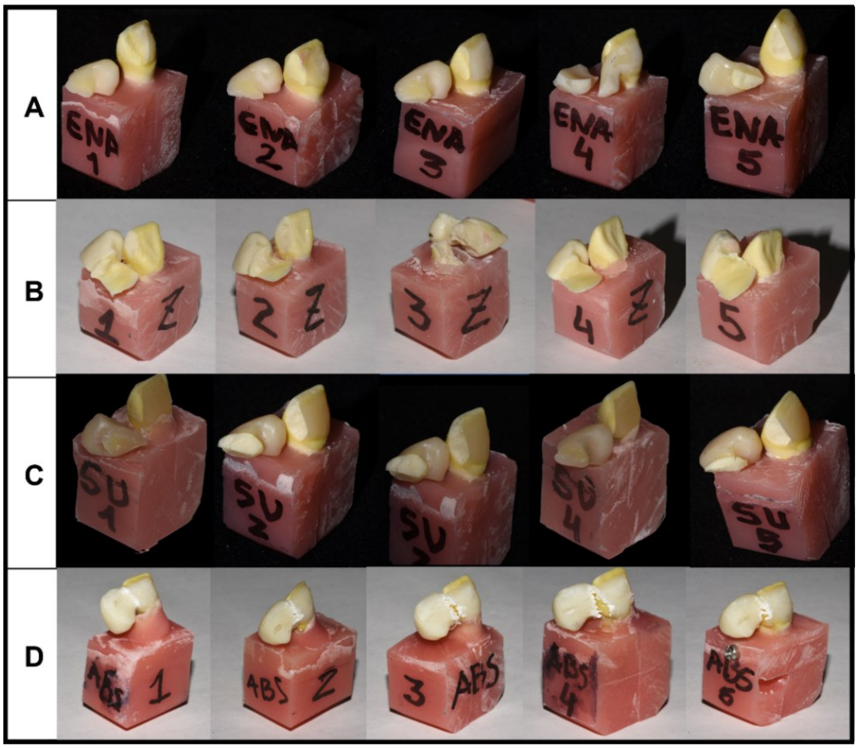

Figure 59 - RBBs after testing. (A) Enamic, (B) Y-ZPT, (C) Suprinity, (D) ABS groups, with different mechanical behavior after shear load

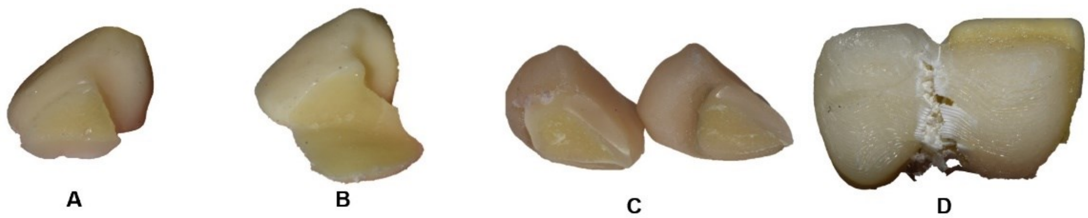

Figure 60 - Details of fractured RBBs and the most frequent mode of failure by material type. (A) ENA, adhesive on the interproximal surface and cohesive in the retainer; (B) Y-ZPT, adhesive with RBB integrity; (C) SUP, cohesive in Frasaco tooth and retainer; (D) ABS, adhesive on the interproximal, cohesive with plastic deformation in RBB

A study focusing on the maximum bite force (MBF) (maximum occlusal force that a person can create during biting), refers to that it is around 80 N (20% higher in bruxists) in individuals aged from 22-48 years old.[197] It varies with malocclusion, sex (higher in males), and age (increase until young adult age), decreasing significantly with vertical and transverse craniofacial and dental discrepancies, and with old age.[198,199] Patients with normal sagittal occlusion are expected to have more molar bite force than patients with different malocclusions, with a magnitude 2 to 3 times greater in the molar region compared to the anterior region.[200] Data from a recent systematic analysis showed that MBF ranged from 246.22–489.35 N and 5.69–16.1 kg in children and adolescents.[201] If we directly convert those values to MPa assuming an area of 1 mm^2, respective values of 246-489 MPa and 56-158[202] would be obtained. From a study[202] that used the T-scan to measure the occlusal contact area in MBF, a mean value of 155mm^2 was obtained for healthy young adults, a value that allows conversion to 0.3-3 MPa by mm^2 of contact area.

When focusing on patients treated for MLIA with space opening, reflection must be made because whenever a hypo-divergence is present, higher occlusal loads than the average patient are expected.[203] Meanwhile, at the end of orthodontic treatment, an equilibrated occlusal function is mandatory, distributing occlusal forces, thus reducing the adhesive stress of RBBs in the anterior maxilla.

The results obtained can be extrapolated to clinical situations, as they suggest that monolithic Y-ZPT CAD-CAM RBBs are the most suitable for MLIA rehabilitations, which is consistent with the literature. However, more research is needed for newer zirconias with higher Yitria content because they have approximately half of the toughness according to the manufacturer. However, for practical clinical reasons, if the option is a short-term interim rehabilitation (orthodontic appliance removal or adaptation, periodontal remodeling or maturation, a short period between the end of orthodontic treatment and implant-supported crown placement, or even during the time of osseointegration of the implant), any of the other options will be feasible. However, the option of a printed ABS RBB turns out to be the most interesting, as it can be executed in a short time, at a very low cost, at the chairside, and only needs a hydrophobic resin as surface treatment.

Clinical relevance: Resin-bonded bridges of Vita Y-ZPT, Enamic Suprinity, and 3D printed ABS are capable of supporting the physiological occlusal loads of the anterior maxilla, the first as a definitive, and the others as interim options to rehabilitate MLIA in clinical situations. The option for each will be conditioned by the prevision of the time of use and the necessity to be removed for orthodontic device adaptations or surgical techniques.

4 Global considerations

4.1 Assessing the problem

MLIA is a complex clinical situation with major therapeutic challenges. It often has a genetic origin, presenting familial aggregation, but can arise as a new genetic mutation.[204] If we think its diagnosis is made at an age of great craniofacial growth, it is easy to infer that in cases with the indication for orthodontic treatment with opening of the space for the missing tooth, we will sometimes have a time window of more than a decade between diagnosis and definitive rehabilitative treatment with an implant.[205] Thus, whenever the clinician diagnoses a case of MLIA, a conflict arises between treating soon after diagnosis or delaying treatment until a stabilized growth phase is achieved. In dental agenesis, the second premolars and lateral incisors are the most frequently missing teeth (incisor-premolar hypodontia).[7,8,11] Additionally, patients with agenesis of second premolars have a significantly higher prevalence of microdontia of maxillary lateral incisors.[9] Severe hypodontia cases often include agenesis of the maxillary lateral incisor and both premolars.[8,10] Some of those subjects were extensively evaluated in the Introduction section of **Paper 1**.

Another question that arises after performing the treatment with the opening of the space is how to maintain the obtained space for an extended period. The esthetic, functional, osseous, and periodontal aspects condition the choice, aiming for rehabilitation that looks like a natural tooth. **Paper 2** analyzed research papers that addressed esthetic aspects related to the options to close or to open the MLIA space, according to observers with training in dentistry or laypeople.

Ideally, resin-adhered bridges, preferably with a single wing or retainer, would be the treatment of choice. However, this option depends on the strength of the restorative materials and the adhesive protocol to be chosen for each potential material. CAD-CAM monolithic zirconias are the toughest materials among today's CAD-CAM monolithic ceramics but also the ones presenting greater uncertainties of predictable adhesion to dental structures and with more complex adhesive protocols. In **Papers 3** and **4**, systematic reviews and meta-analyses of the data on the different available CAD-CAM materials and their potential for use in the rehabilitation of MLIA and contemporary luting cements were performed. The knowledge acquired in the preparation of those four papers was complemented by an extensive specific literature review for these in the areas of CAD-CAM monolithic ceramics, fundamental concepts of adhesion, and, in particular, all the parameters involved in the adhesion of restorative materials to dental structures, information that is resumed in **Chapter 2**.

4.2 Searching for a solution

With some ideas in mind, this work was carried out with the concern of developing an experimental part well-grounded in theoretical concepts. Behind this, there was always a motivation to find a solution with immediate clinical application in situations of MLIA treated by space opening.

Evidence suggests that to best predict the future clinical performance of a rehabilitation device, its design should match as closely as possible the anticipated clinical design in terms of full anatomy, variations in interproximal wall length, core shape and thickness, and veneer thickness. Furthermore, its fabrication procedures should be similar to the usual laboratory and clinical procedures and the supporting structures that will be used clinically should be anticipated. Fatigue loading in water with sliding contacts is also pertinent.[36]

That said, laboratory studies only make sense if they are hypothetically used in the clinical context. After reviewing the accessible literature on the materials evaluated in this work in **papers 3** and **4**, we concluded that existing research focuses mainly on adhered restorations as a whole, on the cement-tooth interface, or the cement–restoration interface. To overcome this fact, we propose to study step by step all the components involved in rehabilitating an MLIA clinical situation with a resin-bonded bridge manufactured with the selected CAD-CAM materials because the bond strength depends on which CAD-CAM block is evaluated, on the surface treatment and on which adhesive cement is used, parameters scrutinized in **Papers 3** and **4**.

During the preliminary tests reported in **Paper 5**, it was possible to identify several constraints regarding the assembly of the specimens. It was especially difficult to achieve parallelism between the bases and the cylinders during cementation. Perhaps this was the reason for the pretest failures found in the Y-ZPT and Suprinity groups. Standardization of procedures was an evolutive process but was crucial to reduce the bias of results for technical errors to the minimum possible. It was also satisfactory to confirm that experimental protocols based on everyday clinical procedures, performed with equipment available in an average dental office, produced similar results to those performed with expensive laboratory equipment frequently reported in the literature, which, in turn, do not match dental cabinet equipment.

To pursue the main goal of the present study, which was to analyze the in vitro performance of some monolithic ceramic materials that could be used to fabricate resin-bonded fixed dental bridges (RBB) to rehabilitate specific patients with agenesis of the maxillary lateral incisor (MLIA), we built a progressive strategy from the basic to the more complex search for an adequate solution, not only mechanically speaking but also easy to handle, and if possible easily affordable. The candidate RRBs for this final solution were evaluated in the last experimental task (5), which is the result of the knowledge acquired during this work, and the details are fully accessible in **Paper 7**.

The specific objectives of this work were achieved and are described in detail in the experimental articles. The study reported in **Paper 5** evaluated the shear strength of the different monolithic ceramics. It was already intended at this stage to be able to combine different adhesive cements with different ceramics. However, the initial difficulties in building an effective experimental model led us to be humbler and develop partial goals. Despite that, by crossing the results from microscopy and surface energy data, we confirmed HF 5% as a suitable treatment to prepare the surface of Vita Suprinity and the dependence of Vita ENAMIC and Vita Y-ZPT zirconia on chemical reactions. The mean ± standard deviation for the shear bond strength was resin-matrix composite (69.10 ± 24.58 MPa) > Vita Y-ZT zirconia (18.48 ± 12.12 MPa) > VITA Enamic (18.38 ± 8.51 MPa) > VITA Suprinity (11.44 ± 4.04 MPa), confirming that other factors in addition to toughness must be addressed when trying to find a better solution to rehabilitate a case of MLIA with an RBB. An aspect to be evaluated in the future is the superior performance of the manually made cylinders of the resin-matrix composite. This group was the first to be assembled, but the storage conditions and timing of testing were kept equal for all groups. As the cement used in this task was photopolymerized and not used in self-cured mode, chemical issues originating from immediate strong bonds between those two resin-matrix-based materials are probably responsible for the high performance. The innovation of Task 2.1, reflected in

Paper 5, was the testing of a polymer-infiltrated CAD-CAM ceramic as a potential substitute for natural teeth in shear strength tests. Its mixed chemical composition (polymer and ceramic) allows for a behavior similar to that of a natural tooth, which makes it a potential adherend for shear bond tests. The experimental methodology followed strict control and was reported pedagogically throughout the paper.

To select the best adhesive strategy to lute the selected CAD-CAM monolithic ceramics, a specific task was developed. To obtain maximal standardization, the option was to use the hybrid ceramic Vita Enamic as the base adherend, based on the results from the previous task. **Paper 6** describes in detail the study, but from the data obtained, the association of Rely X Ultimate (RU) cement with Monobond Plus (MB) coupling agent was the most efficient in terms of shear bond strength ($p<.001$) (55.56 ± 4.29 MPa). Vita Adiva IA-CEM (25.07 ± 3.45 MPa) performed better with MB and Panavia SA (35.18 ± 4.77 MPa) with Vita Adiva Ceramic Primer (CP). CP (35.18 ± 4.77 MPa) > MB (28.74 ± 3.23 MPa) increased the strength of the Panavia SA shear bond (SBS) compared to the self-adhesive mode (19.09 ± 6.85), suggesting the use of a coupling agent, which is somehow a paradox. The presence of no direct influence on the SBS by the surface energy of the substrates was also of notice. Furthermore, we found the fluorescence of RU to be helpful in excess removal, and that the polymerization efficacy of Vita Adiva IA-CEM raised doubts, a finding that should be evaluated in the future. Except for SA/0, all combinations tested achieved SBS values within those aimed at adhesion to tooth substrates. As RU performed better than the other cements with both coupling agents, it was selected as a positive reference for the next tasks.

Aware of the difficulty in standardizing procedures and achieving predictable adherend bases, we set out to better study two artificial substrates as base adherends (Vita Enamic and FRASACO teeth) and to compare their adhesive performance with that of natural teeth. For this, two tasks were developed, one performed with Frasaco teeth using a protocol similar to the studies done in task 2.1 but without including the discarded Vita Adiva IA-CEM, and another where the shear strength of the cements adhered to the natural tooth was assessed. Finally, a comparison was made between the three adherends results). From the results obtained, we can say that any of these materials may be interesting as an adherend base to be used in future studies. However, there are significant differences between them, especially when we compare the performance of Vita Enamic with that of

FRASACO teeth or even with those results obtained with natural teeth. In the latter case, results bias caused by the fact that the teeth were not fresh must be considered. Despite the tasks being completed, the articles are still in draft (Papers 8 and 10).

As we acquired knowledge and grounded the experimental part of this work, we questioned some of our options. In Task 4 we developed a new experimental model with modified load settings and space between the support bases, to get as close as possible to a situation of rehabilitation of an MLIA by opening the space. In this task, we also determine the compressive strength of the materials tested as a way to validate concepts, because not always the manufacturer's information matches what we find or determine with our equipment. This task is completed and its description and results are in an advanced stage of drafting (Paper 9). The results of this task are of clinical relevance as they validate a new model and provide results that can be used in future modeling of adhesive protocols for prosthetic RBBs made with CAD-CAM materials. For future studies, it would be interesting to evaluate the effect of the different adhesive protocols on the mechanical performance of other materials, namely emerging 3D printed materials. Furthermore, the evaluation of the shear bond strength of the ceramic-adhesive-ceramic assembly under different stress conditions should be considered.

For task 5 a model of adhesive prosthesis with only one retainer (single-retainer RBB) was designed and manufactured in 4 different materials. According to the literature and as proposed from the beginning, the zirconia RBB was considered the reference. This type of material is known for its mechanical resistance, but also for the difficulty of effective adhesion to the tooth, which has motivated an incessant search for the best adhesive protocol, particularly for surface treatment. Recently, some aspects have been elucidated. However, the ideal treatment has not yet been achieved. For this fact knowing the clinical success of fixed prostheses with 3 elements made in zirconia, we decided to design a bridge with a single retainer to adhere to the palatine face of the central incisor, adjacent to the site of agenesis, without any dental preparation but just with very superficial grinding (no preparation) of the dental surface.

When one speaks of the longevity of a rehabilitative treatment, one implicitly thinks of definitive rehabilitation. However, when treating patients with MLIA, the rehabilitative treatment is often intended to be temporary, and above all, adaptable over time. This is the case for example of an orthodontic with space opening, in which the success of the same is reflected by the progressive opening of diastema with the canine tooth. In these specific cases, it will be unthinkable to use an RBB made of zirconia because it is too hard to be removed repeatedly without damaging the supporting tooth and has a complex adhesive technique that hinders the addition of resinous matrix-based materials. Thus, the possibility of performing RBBs with materials of easier handling, more frequent replacement at low cost, or easier removal of the supporting tooth led us to look for other alternatives, especially focused on the management of orthodontic treatments using aligners.

Besides, literature revealed that continuous facial skeletal growth and teeth eruption are very evident in the second and third decades, and can last even to the fourth and fifth decades of life, making it very reasonable to delay the placement of an anterior maxillary implant in the adolescent patient, and first consider a long-term transitional restoration.[206]

Vita Enamic was selected for ease of manufacturing and the results obtained in all previous tests of shear bond strength. Vita Suprinity presented itself as a potential material for its mechanical, esthetic, and finishing strength, although from the beginning there were some doubts as to its superiority in terms of mechanical strength in this experimental model. Medical ABS has recently emerged as a somewhat innovative material ready for complete digital workflow procedures, easy manufacturing, and low cost. To our knowledge, there has been no research on this material for this purpose. Detailed information on this task is accessible in **Paper 7**.

The concept of minimally invasive preparation (non-prep restoration) implicitly presupposes the restriction of the same to the enamel. For this reason, in our studies, the analysis of hydrothermal stress was not considered, as the bond to enamel is quite stable over time.[82] It is possible that our findings are not directly transposable when tooth preparation involves dentin, because it has a surface microarchitecture, a tubular structure, and intrinsic moisture not comparable to that of enamel.[82]

4.3 Final remarks

As a final unifying message of all this work, it could be said that if something has been done, much remains to be done, because the transposition into clinical situations of the results obtained in laboratory studies is not an easy task. There are ethical constraints, allied to time, which make this transposition a work of giants since the huge interindividual variability of MLIA cases and the fast technological evolution related to rehabilitative materials and their adhesive agents make clinical works turn out to be mostly retrospective or else short duration.

When we review the literature, very rarely do randomized clinical trials appear with an observational time of more than 36 months, which contrasts with the accepted time of 10 years as the one that defines the success of treatment in clinical terms. Another field where still little has been done concerning the materials assessed in this work is the fractographic analysis usually reduced to classification as cohesive, adhesive, or mixed. It would be interesting to perform an effective analysis identifying the origin of the fracture (initiation of the crack), the direction and pattern of propagation of the crack, and the energy of the fracture (brittle or ductile; single event or fatigue) and the phases included along the fracture plane to better understand the adhesive joints of dental materials.

5 Conclusions

This work is a combination of tasks and therefore, the conclusions will be divided into four main sections focused on CAD-CAM materials, adhesive cements and protocols, base adherends for shear bond tests, and RBBs for MLIA rehabilitation.

5.1 Mechanical behavior of CAD-CAM materials

The Vita ENAMIC hybrid ceramic as a restorative material was predictable and easy to handle, with a compressive strain of 294±66 MPa, and a shear bond strength when bonded to a resin matrix cement from 19.09±6.85 MPa (Panavia SA/no coupling agent) to 55.6 ±4.29 MPa (Rely X Ultimate/Monobond Plus).

The Vita SUPRINITY zirconia reinforced glass ceramic was brittle in both the pre-sintered and sintered states, difficult to handle, and had the most inconstant performance. It has a compressive strain of 522±274 MPa.

Vita Y-ZT was confirmed as the toughest material but was seldom the best performing because of adhesive failures. The mode of failure with Vita Y-ZT zirconia was always adhesive, highlighting uncertainties about the efficiency of the adhesive joint of this material in the absence of macromechanical retention. It has a compressive strain > 1225 MPa.

When used as RBB simulators adhered to a hybrid ceramic base, their mean best adhesive strength was as (1) cylinders (lateral load), Vita ENAMIC 18.38±8.51 MPa, Vita SUPRINITY 11.44±4.02 MPa, and Vita Y-ZT18.48±12.12 MPa, and as (2) bars (vertical load), Vita ENAMIC 30.9±7.40 MPa, Vita SUPRINITY 24.6±15.2 MPa, and Vita Y-ZT 18.10±6.0 MPa.

5.2 Adhesive cements and protocols

The best-performing adhesive cement was the dual-cure Rely X Ultimate in a 3-step adhesive strategy. Associated with Monobond Plus it reached 55.56±4.29 MPa adhered to hybrid ceramic, 10.40±2.42 MPa to FRASACO tooth, and 18.33±5.09 MPa to natural tooth

Panavia SA in self-etch mode (SA/0, 19.09 ± 6.85 MPa) performed worse than if associated with Monobond Plus (SA/MB, 28.74 ± 3.23 MPa) or the Vita Adiva Ceramic primer (SA/CP, 35.18 ± 4.77 MPa). Although the values attained suggest that it could be used in clinical situations that are not defying in terms of occlusal function, or short or not retentive dental structure.

The Vita Adiva IA-Cem associated with the manufacturer's recommended primer, the Vita Adiva Ceramic primer reached an adhesive strength of 22.68 ± 5.81 MPa, which was lower than that of the universal Monobond Plus 25.07 ± 3.45 MPa, although the difference is not significant.

The efficacy of IA-Cem polymerization raised doubts, because even with an extended initial photoactivation time (60 s), being a dual cure cement, the portions remained unpolymerized after 12 h in self-cure mode.

The fluorescence of RU was helpful for excess removal.

No relation was found between shear bond strength and the surface energy of the substrates, the failure mode was material dependent, and differences in behavior concerning shear forces were easily identified between CAD-CAM ceramics.

5.3 Potential base adherends for shear bond tests

The VITA Enamic block resists a shear load of up to 100 MPa in a design consisting of a cylinder with a double interface connection, so it appears as a potential base adherend for SBS tests.

Frasaco teeth adhered to cement cylinders had a maximum adhesive strength of 10.40 ± 2.42 MPa (Rely X Ultimate/5 % hydrofluoric acid/Monobond Plus) but the relative mechanical behavior for each adhesive protocol was similar to those with hybrid ceramic and natural teeth as adherends.

Unlike hybrid ceramic, for the FRASACO tooth, the aluminum oxide blasting (Al_2O_3, 50μm, 0.20 MPa, 10s) was the best surface treatment to work with Panavia SA in the self-curing mode (9.29 ± 1.58MPa), rather than just grinding (4.24 ± 1.45MPa), or 5% hydrofluoric acid (5.69 ± 3.87MPa).

Vita Enamic hybrid ceramic, by its mechanical properties, and the FRASACO tooth, by its advantageous anatomy despite its lower mechanical properties, are substrates to be considered at least for preliminary shear bond strength tests, because they allow overcoming ethical restrictions and biases for using biological substrates. For a specific adhesive protocol, the shear bond strength of natural teeth was around double that of Frasaco teeth but was half compared to hybrid ceramic.

5.4 Potential RBBs for MLIA rehabilitation

The adhesive strength of the RBBs was dependent on the type of material.

The SBS results indicated that the Y-ZPT RBBs had the highest bond strength among the tested materials (ENA, 24.24 ± 9.05 MPa < ABS, 24.01 ± 1.94 MPa < SUP, 29.17 ± 4.78 MPa < Y-ZPT, 37.43 ± 12.20 MPa). The failure modes were mainly adhesive for Y-ZPT, cohesive for SUP and ENA, and cohesive with plastic deformation for ABS. If the material were ENA or SUP, the fracture led to the complete loss of the pontic which would imply the manufacture of a new restoration. In the case of Y-ZPT the loss of adhesion without structural change would allow a new adhesive procedure.

The plastic deformation Medical ABS probably would allow the patient to have an appointment with his dentist before the loss of the pontic. For definitive rehabilitation, the toughness and the possibility of fabricating very thin retainers make the Y-ZPT the first option to be considered. If the option is a short-term interim rehabilitation any of the other options will be feasible. As an easy changeable option, the printed ABS RBB turns out to be the most interesting, as it can be executed in a short time, at a very low cost, at the chairside, and only needs a hydrophobic resin as surface treatment.

More research is necessary to evaluate the newer, less tough zirconias with higher yttria content.

6 FUTURE PERSPECTIVES

- In vivo evaluation of the performance of the resin-bonded bridgework used to substitute a missing lateral incisor, after orthodontic space opening, according to anatomic, esthetic, and functional parameters, over time.
- Clinical evaluation of marginal adaptation of monolithic ceramic RBBs with connector design and width variation.
- Development of an efficient virtual prototyping method to compare different preparation designs of ceramic resin-bonded bridgework.
- Examination of the effect of connector design and width on occlusal fracture resistance of monolithic ceramic RBBs.

6.1 In vivo resin-bonded bridges evaluation

MLIA patients, treated by space opening, split into two groups, after clinical characterization, in implant [IM] or RBBs [RB] group, considering defined independent variables and conditioning factors.

Exclusion criteria: history of anterior dental trauma, extensively restored abutment teeth.

Photographic protocol, intraoral scanning, radiographic protocol, digital smile simulation, and periodontal status, will be made.

RB group rehabilitation, based on clinical criteria, with the assumed appropriate RBB.

An experienced dentist, an expert in adhesive techniques, will perform a meticulous bonding of the selected RBB, after verification of the CAD-CAM bridge fit.

Adherend substrate preparation and adhesion according to the findings of this work will be delivered to the patients. Global occlusion and canine and anterior guidance will be checked. At 0-, 12- and 24-months, intraoral scanning and photographic protocol will be taken, at clinical follow-up appointments.

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Obtained clinical parameters will allow a patient database for further studies. Ethical approval and informed consent will be mandatory steps of this research.

6.2 Adhesive joint static tests modeling

The costs and risks involved in in vivo studies favor numeric models and in vitro simulation approaches are raising interest among scientists.[207] The biomedical industry has long benefited from virtual prototyping using finite element analysis (FEA) to improve products. In addition, applying FEA allows the calculation of the stress and strain within the tooth structure and biomaterials.[208] Until now, only a few FEA studies have assessed tooth preparation designs using models of all-ceramic RBBs with these new materials.

The objective is to model the RBBs static results obtained in tasks 2-5. Modeling will be done by a finite element analysis using a damage mechanics approach, in the finite element ABAQUS®. A triangular law will be assumed for the cohesive zone model shape. Cohesive elements will be used for all the types of ceramics, used in this study, allowing the numerical prediction of the failure path obtained experimentally. The cohesive properties of the materials will be those determined by the present work standard fracture tests. The numerical load-displacement curves of the static tests will be compared with the experimental results for validation of the damage properties.

Similar adhesive joint mechanical characterization as in task 5, with an angular (45°) loading force instead, applied centrically 2 mm under the incisal border of the lateral incisor is also aimed.

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Original papers

Infraocclusion level and root resorption of the primary molar in second premolar agenesis: A retrospective cross-sectional study in the Portuguese population

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Abstract

Background. Mandibular second premolar (M2P) agenesis results in the second primary molar (2pm) retention, infraocclusion, a reduced alveolar height and width, the supraeruption of antagonists, or the movement of the adjacent teeth. Infraocclusion affects the survival of the retained 2pm to a greater extent than root resorption.

Objectives. The aim of the study was to evaluate the lifespan of the primary molar as a substitute, with root quality and occlusal adaptation, in cases of M2P agenesis in a low-income population to determine if the attitude of just vigilance could be the best clinical option whenever other clinical problems are absent.

Material and methods. A total of 12,949 orthopantomograms were analyzed. Sixty-one patients (25 males and 36 females aged 7–36 years) were divided into group 1 (the first permanent molar in occlusion) and group 2 (the second permanent molar also in occlusion). Vertical positioning to the occlusal plane, root condition and the movement of the adjacent teeth were evaluated.

Results. Despite the study having a cross-sectional design, root resorption, infraocclusion, the distance between the first permanent molar and the first primary molar or the first permanent premolar, and the width of the 2pm were correlated with age. The 2pm root resorption increased with age, which was more pronounced when the second permanent molar was also in occlusion. The mesial movement of the adjacent teeth was absent in all groups. The 2pm was often occluded, but infraocclusion increased with age. Age periods of 11–15 years and 21–25 years were critical for the primary tooth loss.

Conclusions. The second primary molar remains functional in the mandibular arch for up to 25 years. A well-documented no-intervention attitude based on clinical and radiographic data must be weighed in cases without orthodontic issues or with financial constraints.

Keywords: root resorption, infraocclusion, second primary molar, second premolar agenesis, mesial movement

Introduction

Dental agenesis occurs in primary and permanent dentition, usually in the case of third molars, mandibular second premolars, maxillary lateral incisors, and maxillary second premolars,[1–3] as a sporadic, spontaneous de novo mutation[4] or as familial hypodontia, mainly due to autosomal dominant inheritance,[5] but also as part of a syndromic condition,[6] as a phenotypic feature of common conditions, such as Down syndrome or ectodermal dysplasia,[7,8] isolated or as part of complex syndromes, like labiopalatal cleft[8,9] or oral-facial-digital syndrome type I.[7,10]

Other causative factors are environmental factors (radiotherapy, chemotherapy, the disease or infection of the primary tooth, tobacco consumption) or host factors (a viral infection during pregnancy, metabolic imbalance).[11,12]

Different genes are linked with tooth agenesis, including *AXIN2*, *IRF6*, *FGFR1*, *MSX1*, *PAX9*, and *TGFA*.[13,14] To date, several single-nucleotide polymorphisms (SNPs) and mutations influencing the function of *AXIN2* have been identified and related to both tooth agenesis and colorectal or hepatocellular carcinoma, or prostate, ovary or lung cancer. This supports the hypothesis that missing teeth can be a marker for predisposition to cancer.[9,13] Agenesis can be diagnosed early in life, allowing the implementation of surveillance programs,[15,16] as in the case of the demonstrated positive correlation in a three-generation family with an *AXIN2* variant and a history of colorectal cancer, colon polyps and tooth agenesis, probably more as an associated event than as a causative one.[17]

The prevalence and severity of dental anomalies are high in humans, and seem jaw- and location-dependent, as most dental anomalies in the maxilla involve the anterior region, and in contrast, the opposite occurs in the mandible, which can be possibly explained by different evolutionary history and ontogeny.[18] Non-syndromic orofacial clefts are frequently associated with tooth abnormalities other than agenesis, such as supernumerary teeth, developmental enamel defects, microdontia, peg-shaped anterior teeth, taurodontism, tooth malposition and/or transposition, tooth rotation, or tooth impaction, but no association with fusion and/or germination has been observed.[19]

There is evidence of an association between the nutritional status, specifically vitamin D and calcium levels, and severe early childhood caries (S-ECC) in preschool children.[20] Still, in severe vitamin D deficiency, there is a high risk of non-syndromic amelogenesis imperfecta and dentinogenesis imperfecta, enamel hypoplasia, hypomineralization/maturation defects, and the abnormal shapes of permanent teeth.[21] When present, developmental enamel defects are also frequently associated with dental caries in preschool children,[22] and clinically occur with discoloration and esthetics problems, tooth sensitivity, wear, and erosion.[23] The main goals of monitoring tooth developmental abnormalities are an early diagnosis, the improvement of appearance and function, the preservation of dentition, the prevention of complications, and the improvement of quality of life.[24] The least invasive treatment possible contributes to pulp protection without a further loss of hard tissues, delaying more invasive treatment options as long as possible. Remineralization products alone or combined with CO_2 laser irradiation,[25] or CO_2 laser irradiation in different protocols, and resin composites or modified glass ionomer restorations have been suggested to treat the dentinal hypersensitivity associated with dental structure abnormalities.[26,27]

Mandibular premolar agenesis has been reported as the most common agenesis just after third molars, ranging from 2.4% to 4.3%,[28,29] with ethnic[3,30] and gender[31] variations, revealing its genetic origin,[4,6] as reported worldwide.[3,6,30–32] Mandibular second premolar (M2P) agenesis occurs mainly with the retention and infraocclusion of the second primary molar (2pm),[33] the loss of alveolar height and width, antagonist supraeruption, and the movement of the adjacent teeth, with a possible negative influence on the sagittal and vertical dentofacial development, and increased overbites.[34–36] The loss of space and the retention of the first premolars can also occur.[28]

The 2pm has been described as having one of the longest lifespans.[37] Its infraocclusion and root resorption, or the mesial movement of the adjacent teeth seem to slightly increase after 20.[38] When present, infraocclusion worsens the prognosis more than root resorption.[39] If the 2pm is retained for a long time, its occlusal relationships must be considered, since adequate and well-distributed occlusal forces are crucial for extended survival.[40] The correlation of longevity with the presence or absence of the second permanent molar may also be pertinent.

M2P agenesis should alert to clinically important tooth anomalies, such as an increased risk of agenesis of other permanent teeth, the transposition of incisors, impaction, delayed tooth development, ectopic eruption, retained primary teeth, and different tooth size or shape abnormalities.[33,41–43]

When treating a skeletal malocclusion, it is difficult to predict the final facial growth, and the challenge becomes even greater in the presence of dental anomalies, which compromise normal function and esthetics.[44] Articles specifically relating M2P agenesis to skeletal malocclusions are extremely rare and performed in the populations seeking orthodontic treatment. Data reveals inconsistency and dependency on ethnicity. That said, there seems to be some tendency to associate M2P agenesis with Class III[44,45] or Class II/div 2[1,46] skeletal malocclusions, and with a hypodivergent growth pattern.

The diagnosis of tooth agenesis and treatment planning involve clinical evaluation and radiographic confirmation.[47] Radiographic parameters are usually obtained from orthopantomography,[42,43,48] lateral cephalograms,[49] bitewing or periapical radiographs,[50] and cone-beam computed tomography (CBCT) if the conventional radiography fails to provide a correct diagnosis, but not as a standard method of diagnosis,[51] considering a more significant radiation risk[52] and a higher economic cost relative to the conventional radiography.[53] In cases with palatal clefts involving complex decisions, like osseous grafts or the need to preserve crucial anatomic structures, CBCT may be required. Combining low mAs (16) and kVp (70) with a small voxel size (180 μm) enables the association of a low effective dose with high image quality.[54] More recently, the possibility of using magnetic resonance imaging (MRI) as a feasible tool for orthodontic treatment planning without radiation exposure has been described, through transforming the acquired data into lateral cephalograms, allowing reliable measurements, similar to those applied in orthodontics routine or related disciplines, such as orthognathic surgery, despite the need for specific post-processing software and an experienced user.[55] Magnetic resonance imaging may also be an alternative diagnostic tool for three-dimensional (3D) cephalometric analysis, with an excellent agreement with the reference measurements of CBCT, the accepted gold standard for 3D cephalometric analysis.[56]

The careful examination of orthopantomograms identifies abnormalities in number (hypodontia, oligodontia and hyperdontia), size (microdontia and macrodontia), structure (amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia), position (transposition, ectopia, displacement, impaction, and inversion), and shape (fusion/germination, dilaceration and taurodontism), most of them asymptomatic.[57] Such data is precious in syndromic patients,[10,58] as these patients need periodical dental and orthodontic supervision to prevent or control the subsequent oral problems.

The early detection of agenesis is crucial for an appropriate and reasonable interceptive treatment plan for a missing M2P.[49] Mandibular post-rotation and the increased total gonial angle associated with infraocclusion have been described, reinforcing the need for an early diagnosis[59] and the intervention of a multidisciplinary team.[60] The 2pm retention, with or without infraocclusion, with the absence of M2P agenesis must be wisely identified, as a treatment plan in the presence of ankylosis is more or less ascertained.[61] Meanwhile, the extraction of the 2pm with a missing M2P may offer benefits, such as avoiding prosthetic replacement, and reducing or eliminating the need for orthodontic appliances once spontaneous space closure occurs, especially if the second permanent molar has not yet erupted.[62]

In cases with dental crowding, autotransplantation must be considered, as it may have a good prognosis, provided it is carefully planned and timed. In growing individuals, the transplanted tooth enables the growth and development of the alveolar ridge, and may offer a permanent solution to agenesis,[63] mainly because the implant survival in children under the age of 13 is low, with most losses occurring early during the healing phase.[64] Moreover, espite decreased passive eruption in patients over 15,[65] replacement with an implant must be well-weighed, as using implants in growing children is controversial,[66] and to overcome in the future the infraocclusion of the implant-supported crown, a new restoration, orthodontic treatment, distraction osteogenesis, or coronal implant placement is often recommended.[67] Furthermore, patients with M2P agenesis have narrower and shorter mandibular cross-sections than a control group, with pronounced lingual alveolar plate and submandibular fossa, enhancing the risk of bone perforation during endosseous replacement (tooth autotransplantation or implant installation).[68] However, this constraint can be minimized with a well-established osseous diagnosis and a 3D additive manufacturing technology.[69]

A fixed prosthesis, either as a permanent partial bridge or a semi-permanent resin-bonded bridge, like an implant, restrains the growth of the alveolar process, not being a perfect solution. Despite not being focused on M2P agenesis, a study by Cahuana-Bartra et al. revealed that patients with hypodontia showed satisfaction with resin-bonded bridges over a 7-year observation period, with an 88% success.[70]

Regarding treatment options, data from 42 studies published in the years 1980–2015 presented a mean survival of 95.3%, 94.4%, 89.6%, and 60.2% for implants, autotransplants, retained primary teeth, and the conventional prostheses, respectively.[64] Meanwhile, the mean satisfaction rates for the type of treatment, i.e., for implants, the conventional prostheses, autotransplants, and orthodontic space closure, were 93.4%, 76.6%, 72.0%, and 65.5%, respectively.[64] Yet, in the last two decades, there seems to be a shift in therapeutic decision-making, with a tendency to prefer orthodontic space closure to space opening and prosthetic replacement, perhaps reflecting a greater optimism with biomechanical strategies since the implementation of temporary anchorage devices (TADs) to assist in space closure, especially if the agenesis is asymmetrical,[71] as TAD-assisted space closure can be considered a safe treatment option for young patients with M2P agenesis.[72] Autotransplants and deciduous teeth were reported to have low annual failure rates,[64] and seem appropriate for children and adolescents at a low cost.The review found a mean observation time of 4.1 years for children, 4.9 years for adolescents (<18 years) and 6.4 years for adults in the included studies.[64] In cases with the agenesis of multiple teeth, the attachment of an overdenture on the remaining teeth can be considered,[73] provided the daily oral hygiene and routine maintenance are feasible.

Concerning M2P agenesis, despite the agenesis being located posteriorly, the patient's self-image can play an essential role in making clinical treatment decisions and the dentist's esthetic judgment.[74] Patients and their families would probably benefit from an oral health-related quality of life (OHRQoL) questionnaire to accelerate the implementation of treatment. Despite this kind of agenesis being presumably less esthetically compromising, children with oligodontia were described as having poorer scores as compared even to their parents, with no direct relationship with the number of missing teeth, exhibiting significantly worse social well-being scores for anterior agenesis and better ones whenever there was a retained primary tooth, probably masking the effect of the permanent tooth agenesis, especially in younger children.[75] One of the optimum treatment standards in pediatric dentistry is the esthetic demand, which impacts on the child's OHRQoL, and subsequently the child's general health-related quality of life. Thus, it is beneficial to the dentist to identify the influence of esthetic restorations on the OHRQoL of preschool children.[76] The OHRQoL of preschool children treated with zirconia crowns was described as significantly better as compared to those who received resin-bonded composite strip crowns.[77] An adapted and validated Early Childhood Oral Health Impact Scale (ECOHIS) questionnaire could be an excellent tool to distinguish children without agenesis from those with a moderate to high percentage of missing teeth, like it was made for caries experience,[77] or to determine the impact of agenesis treatment on OHRQoL in situations of a low percentage of missing teeth.[78] There is still no evidence of a long-term survival of the mandibular 2pm, and to accurately answer the typical questions from the patient: "For how long can my primary tooth survive if we decide to leave it in situ?" or "Will it be healthy and functional?", is yet tricky.[38] Well-designed longitudinal, prospective controlled studies comparing the advantages and disadvantages of the interceptive extraction of the primary molar or preserving the primary molar as a substitute for the absent permanent tooth in children in the early mixed dentition are an emergent need.[79]

Using video-sharing platforms and virtual social networks can be helpful to spread information among patients. Nevertheless, the information disseminated should be scrutinized and weighed with well-defined criteria,[80,81] and healthcare professionals, academic institutions and professional organizations should direct patients to reliable and more authoritative information sources, allowing consumers to critically assimilate the information posted in order to make effective healthcare decisions.[82,83]

Teledentistry for oral screening, especially in school-based programs, rural areas, and areas with limited access to care, could also be used to identify tooth agenesis. Teleconsultations are possible and valid,[84] if the business model and the cost-effectiveness concerns related to the time spent, particularly in the context of developing countries, are taken into account, as the preferred way seems to be a video-conference, followed by a phone call.[85]

Some of the cases of missing teeth are complex clinical situations that require treatment involving not only the dentist, but also other medical specialists, such as the internist, the neurologist, the psychiatrist, the endocrinologist, the cardiologist, and the dermatologist.[64]

Considering all these concepts, with this study, we aimed to contribute to the understanding of the natural evolution of the second primary molar (2pm) in a population not selected by orthodontic issues, and to estimate the longevity of 2pm, given its root resorption, occlusal positioning and the behavior of the adjacent teeth, with the prospect of finding scientific evidence to encourage its preservation in the oral cavity as a lasting therapeutic option, but also bearing in mind that low-income countries have financial constrains regarding complex treatment, such as orthodontics or implant-supported crowns.

To frame our study theoretically, a mini-narrative review was done.

Material and methods

An observational, cross-sectional and retrospective study was developed by analyzing digital orthopantomograms from the clinical records of outpatients at the Dental Clinic of the University Institute of Health Sciences (IUCS)/CESPU, Gandra, Portugal, from 4 consecutive years (January 2014–December 2017).

The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies were followed. The ethical approval was provided by the Ethics Committee at IUCS/CESPU.

The hypotheses formulated were: H_1 – the second primary molar (2pm) has the root and occlusal conditions to preserve the space corresponding to the absent permanent tooth for at least 15 years; and H_0 – the second primary molar (2pm) does not have the root or occlusal conditions to preserve the space corresponding to the missing permanent tooth.

Study population and data collection

Based on a preliminary sample of 12,949 orthopantomograms, 6,001 (46.34%) from males and 6,948 (53.66%) from females, 61 patients – 25 (40.98%) males and 36 (59.02%) females, aged 7–36 years, with a mean age of 16.38 ±7.96 years – were diagnosed simultaneously with M2P agenesis and the 2pm retention. The 3rd quadrant and the 4th quadrant (tooth 3.5 or 4.5) were registered separately.

Oligodontia, cleft palate, syndromic cases, bone defects, the evidence of surgery or extraction, trauma, fractures, or previous orthodontic treatment were excluded.

Error of the method

The orthopantomograms were acquired with a digital device (PaX-400; Vatech, Hwaseong, South Korea) and after standardized photographic printing, analyzed to determine which teeth were present, absent or extracted. The subsequent measurements were done with an orthodontic ruler (Dentaurum, Ispringen, Germany), following the method of Odeh et al.[86] One investigator systematically observed all orthopantomograms, and a second one blindly and randomly followed half of the sample for calibration and to discuss possible doubts. An administrative employee blindly coded the orthopantomograms to avoid the examination bias. Afterward, the results of the examinations were sorted by groups for statistical comparisons.

Evaluation of the measurement error

In evaluating the intra-observer and inter-observer variability corresponding to the observations of the variables involved in this investigation, 13 randomly selected patients from the initial sample were considered. In the inter-observer variability study, the 13 individuals were evaluated by 2 independent observers. For assessing the intra-observer variability, the investigator performed measurements on the 13 patients on 2 occasions, with a 2-month interval. The variability was evaluated through the intraclass correlation coefficient (ICC) with the determination of the confidence interval (*CI*). Table 1 shows the mean (*M*) and standard deviation (*SD*) values with regard to the examined variables of a quantitative nature, and the respective ICCs assessed by the same investigator (Observer 1).

Similar mean values were observed at both time points. The ICC values were considered high (1 corresponds to a perfect agreement) and very close to each other, revealing a good agreement between the 2 observations for all quantitative variables.

The statistical values (*M* ±*SD*) to assess the inter-observer variability were calculated based on measurements from 2 different investigators (Observer 1 and Observer 2). They are shown in Table 2, together with the ICC values.

Similar mean values were observed for the 2 observers. The ICC values were high and very close to each other, verifying a good agreement for all quantitative variables and suggesting the reliability of the analyzed data.

Table 1. Intra-observer agreement of the variables under study

Variable	Observation 1 *M* ±*SD*	Observation 2 *M* ±*SD*	ICC (95% *CI*)
RR	0.36 ±0.26	0.38 ±0.30	0.950 (0.835–0.985)
Width X [mm]	13.31 ±1.70	13.54 ±1.20	0.935 (0.788–0.980)
Width Y [mm]	10.77 ±2.17	10.84 ±2.30	0.926 (0.759–0.978)
Infraocclusion [mm]	2.46 ±1.07	2.67 ±1.16	0.977 (0.924–0.993)

M – mean; *SD* – standard deviation; ICC – intraclass correlation coefficient; *CI* – confidence interval; RR – root resorption; width X – mesiodistal width of the second primary molar (2pm); width Y – distance between the mesial face of the first permanent molar and the distal face of the first primary molar or the first permanent premolar.

Table 2. Inter-observer agreement of the variables under study

Variable	Observer 1 *M* ±*SD*	Observer 2 *M* ±*SD*	ICC (95% *CI*)
RR	0.37 ±0.26	0.38 ±0.24	0.835 (0.460–0.950)
Width X [mm]	13.31 ±1.70	13.63 ±1.45	0.759 (0.345–0.920)
Width Y [mm]	10.77 ±2.17	10.38 ±1.81	0.926 (0.759–0.978)
Infraocclusion [mm]	2.46 ±1.07	2.46 ±1.05	0.978 (0.925–0.993)

Sample grouping

The groups were as follows: group 1 – the first permanent molar in occlusion (*n* = 23); and group 2 – the second permanent molar also in occlusion (*n* = 38). A subdivision was made to correlate root resorption (RR), width X, width Y, infraocclusion, and age.

Orthopantomography analysis

Methods and tools were defined as follows:

- the degree of RR, evaluated according to a 6-point scale (the Bjerklin and Bennett method[38]) (Fig. 1A), assessing the distal and mesial roots. The highest RR value was scored for the tooth; scores 4, 5 or 6 (i.e., 3/4 of the root or more resorbed) were considered as a poor root condition;
- infraocclusion (the distance from the occlusal plane to the occlusal surface of the 2pm in millimeters) (Kurol's method[87]) (Fig. 1B);
- width Y (the distance between the mesial face of the first permanent molar and the distal face of the first primary molar or the first permanent premolar in millimeters) (Fig. 1C); and
- width X (the mesiodistal width of the 2pm in millimeters) (Fig. 1D).

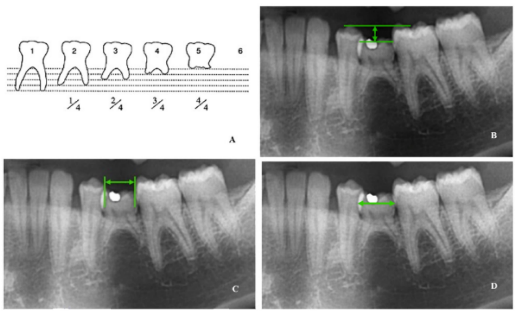

Fig. 1. A – different root resorption (RR) stages, measuring the quarters of each root (adapted from Bjerklin and Bennett (2000)[38]; B – measurement of the primary tooth infraocclusion; C – measurement of width Y; D – measurement of width X

Statistical analysis

The descriptive data was presented as mean and standard deviation (*M* ±*SD*), or as frequency and percentage (*n* (%)). The χ^2 test was used to assess the existence of dependence between 2 qualitative variables. The Monte Carlo simulation techniques were used whenever the applicability conditions of the χ^2 test were not met. Spearman's and/or Pearson's correlation coefficients were used to assess the degree of association between 2 variables (ordinal or continuous). Comparisons between groups, based on quantitative variables, were performed with the use of parametric tests whenever their applicability assumptions were satisfactory; otherwise, nonparametric alternatives were used. The Shapiro–Wilk test assessed the assumption of normality and Levene's test – the homogeneity of variance. A *p*-value ≤0.05 was considered statistically significant. Descriptive, graphical and inferential statistical analyses were performed using the IBM SPSS Statistics for Windows software, v. 20.0 (IBM Corp., Armonk, USA).

Results

Group 1 presented a mean age significantly lower than group 2 (9.39 vs. 20.61 years) ($p < 0.001$).

The prevalence of M2P agenesis associated with the 2pm retention was 0.47% in the total sample, affecting tooth 4.5 in 50.8% ($n = 31$) and tooth 3.5 in 49.2% ($n = 30$) of the cases. The inferential statistical analysis indicated that the percentage of patients affected by tooth 3.5 or 4.5 agenesis was not significantly different from 50.0%, so prevalence was similar in both quadrants.

The RR values were significantly different between the groups ($p = 0.001$). Group 1 had a higher frequency of low values, while group 2 had a higher frequency of values 0.50 (2/4 of RR) and 0.75 (3/4 of RR). The root resorption of the 2pm increased when the second permanent molar was also in occlusion, but it was impossible to detect its ending (Fig. 2A).

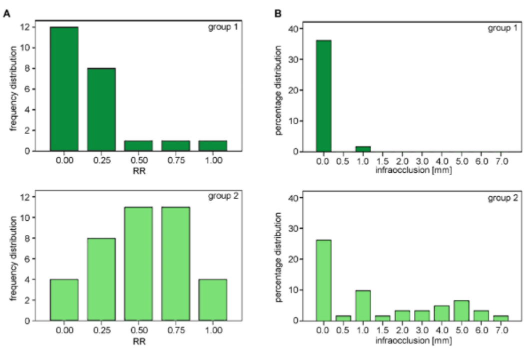

Fig. 2. A – distribution of root resorption (RR) according to group; B – distribution of infraocclusion according to group

Infraocclusion differed significantly between the groups ($p = 0.036$). The most frequent value was 0 mm (in occlusion) for both groups. In group 1, the values ranged from 0 mm to 1 mm, while in group 2 they ranged from 0 mm to 7 mm, being more often 0 mm or 1 mm, but increasing with age (Fig. 2B).

With the fundamental hypothesis being a zero correlation coefficient, the relationship between width X and width Y was compared among the groups. The correlation coefficients and *p*-values associated with the statistical test were calculated (Table 3). The dispersion diagram between width X and width Y according to group is displayed in Fig. 3.

The mean width X was significantly higher than the mean width Y in both groups, so the influence of the group on that difference was analyzed. We found a mean difference between width X and width Y of 2.09 mm in group 1 and of 2.77 mm in group 2. However, the equality between these 2 averages was not rejected ($p = 0.269$) (Table 4).

The correlation coefficients for the variables RR, width X, width Y, and infraocclusion with regard to age were calculated separately in the total sample, group 1 and group 2. Low correlation coefficients were found, significantly different from zero only for the whole sample. The strongest correlation with age was found for RR and infraocclusion. There was also a weak correlation between age and width Y, but still significantly different from zero (Table 5).

Table 3. Relationship between width X and width Y according to group

Statistics	Group 1	Group 2
r	0.408	–0.079
p-value	0.048*	0.639

* statistically significant.

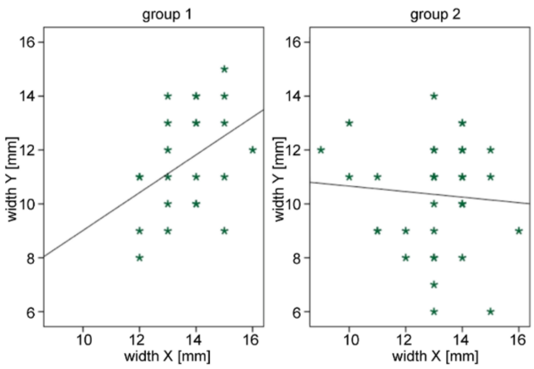

Fig. 3. Dispersion diagram between width X and width Y according to group

Table 4. Comparison between width X and width Y

Group	Width X [mm]	Width Y [mm]	*p*-value
Group 1	13.70 ±1.15	11.61 ±1.97	<0.001*
Group 2	13.11 ±1.97	10.34 ±1.94	<0.001*

Data presented as *M* ±*SD*. * statistically significant.

Table 5. Correlation between the variables root resorption (RR), width X, width Y, and infraocclusion and age

Variable	Total sample		Group 1		Group 2	
	r	*p*-value	r	*p*-value	r	*p*-value
RR	0.408	0.001*	0.066	0.763	−0.112	0.504
Width X	−0.129	0.324	−0.087	0.694	−0.032	0.849
Width Y	−0.261	0.042*	−0.167	0.445	−0.045	0.790
Infraocclusion	0.483	<0.001*	−0.248	0.255	0.142	0.394

* statistically significant.

To confirm those results, age categorization for each group was done to determine how the mean values of RR, width X, width Y, and infraocclusion varied according to age subgroups.

The results are displayed in Tables 6,7 and Fig. 4. In group 1, the mean RR values were similar in both age subgroups, slightly reducing with age. In group 2, the lowest mean RR value was observed for patients over 30, followed by those aged 21–25 years; for subgroup 26–30 years, the mean RR value was similar to those observed in the first 3 age subgroups. Comparing the groups, group 1 presented lower RR values.

In group 2, the mean infraocclusion was approx. 0 mm for patients under 11 years of age, with a progressive increase up to 21–25 years, followed by a decrease with age. In group 1, the average infraocclusion was approx. 0 mm in both age subgroups.

Regarding width X, in group 2, the subgroups up to 20 years and that of 26–30 years showed similar mean values.

Table 6. Root resorption (RR), width X, width Y, and infraocclusion according to age subgroups in group 1 (*n* = 23)

Variable	Age [years]	
	<11 *n* = 19	11–15 *n* = 4
RR	0.20 ±0.23	0.13 ±0.14
Width X [mm]	13.74 ±1.15	13.50 ±1.29
Width Y [mm]	11.68 ±2.06	11.25 ±1.72
Infraocclusion [mm]	0.05 ±0.23	0.00

Data presented as *M* ±*SD*.

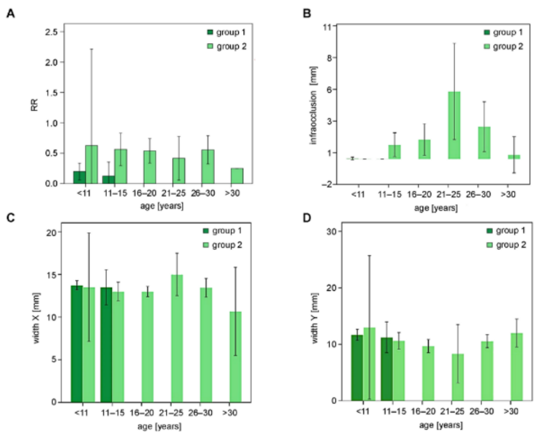

Fig. 4. A – root resorption (RR) according to group and age subgroups; B – infraocclusion according to group and age subgroups; C – width X according to group and age subgroups; D – width Y according to group and age subgroups

The highest value was observed in subgroup 21–25 years and the lowest in patients over 30. In group 1, no differences were found. Globally, group 1 and group 2 did not differ.

Regarding width Y, in group 2, patients under 11 or over 30 showed the highest values, and subgroup 21–25 years showed the lowest value. In group 1, the mean width Y was nearly equal in both subgroups. Globally, group 1 and group 2 did not differ.

No significant movement of the adjacent teeth was observed in any of the groups or subgroups, so the vertical position of the teeth was apparently maintained.

Table 7. Root resorption (RR), width X, width Y, and infraocclusion according to age subgroups in group 2 (*n* = 38)

Variable	Age [years]					
	<11 *n* = 2	11–15 *n* = 8	16–20 *n* = 13	21–25 *n* = 3	26–30 *n* = 9	>30 *n* = 3
RR	0.63 ±0.18	0.56 ±0.32	0.54 ±0.34	0.42 ±0.14	0.56 ±0.30	0.25 ±0.00
Width X [mm]	13.50 ±0.71	13.00 ±1.31	13.00 ±1.00	15.00 ±1.00	13.44 ±2.56	10.67 ±2.08
Width Y [mm]	13.00 ±1.41	10.63 ±1.77	9.69 ±1.93	8.33 ±2.08	10.56 ±1.42	12.00 ±1.00
Infraocclusion [mm]	0.00	1.13 ±1.12	1.54 ±2.08	5.33 ±1.53	2.56 ±2.56	0.33 ±0.58

Data presented as *M* ±*SD*.

Discussion

The clinical decision to treat M2P agenesis associated with the retained 2pm is a challenging issue,[60] and the options to extract, thus allowing space closure, to prosthetically replace the missing tooth or to maintain the primary tooth in the arch implies reflection over various parameters, such as the health of the crown, pulp and root of the primary tooth as well as of the surrounding bone,[50] the vertical position of the primary tooth relative to the occlusal plane; the presence of ankylosis of the primary tooth,[60] the patient's sagittal and vertical skeletal individual characteristics,[62,88] the occlusal relationships and dental crowding, the patient's dental and chronological age,[62] the presence of third molars, and the patient's preference for specific treatment or the expenditure of money.[29,34,35]

Whenever the delayed exfoliation of the 2pm is detected, the diagnosis must necessarily be completed by the radiographic observation and verification of M2P agenesis,[47] as if it occurs, the therapeutic option is an urgent need, and in the majority of the cases, it is a complex therapy.

Based on the literature, globally, we can say that a healthy 2pm with no signs of ankylosis, no carious lesions or extensive restorations could be maintained with the expectation of extended survival. Nevertheless, the anteroposterior arch length discrepancy must be controlled, sometimes by carrying out mesial and distal stripping, with a 2–3-millimeter reduction of the coronal length of the 2pm. One must be careful not to produce pulp lesions and be aware that such treatment is advisable mainly if later replacement with an implant is feasible. We must also be mindful that preserving the 2pm in function can have occlusal repercussions.

Also, in general, patients with minimal crowding, deep overbites, retrusive incisors, decreased lower facial heights, or flat mandibular planes may be candidates for no extraction, maintaining the 2pm for as long as possible. In the case of significant crowding, dental protrusion, minimal overbites or open bites, incisal inclination within a normal range, and increased lower facial heights, patients often benefit from extraction and space closure, but also with the extraction of the remaining 3 second premolars.[89] Meanwhile, based on clinical experience, we are confident that the premolar space closure with the use of an orthodontic device is more cost-effective, mainly if TADs are used to assist in space closure,[71] often without the need for bone grafting, manual bone spreading[90] or osseodensification to increase ridge dimensions in a narrow alveolar ridge[91] before implant placement, or using a prosthetic restoration with inherent costly maintenance as compared to that of a natural tooth.

Bearing in mind those concepts, we chose patients from our University's Dental Clinic as the target population. The only initial requirement was having the digital orthopantomography taken before the first consultation, available in the clinical records. In terms of selection criteria, the population differed from most of the populations from previous studies, as it was a raw population, i.e., it was not related to the orthodontics or various pediatric dentistry departments, so the patients had no prior diagnosis of an orthodontic issue or agenesis. This fact that could contribute to a certain bias.

Another peculiarity is that the average monthly income per capita of that population is less than half the country's mean reference value, which restricts onerous treatment, making the possibility of keeping the 2pm in function for a long time a socially fundamental therapeutic option.

Furthermore, since the clinical decision should be made as early as possible, ideally still in the early pediatric age (<9 years), we did not impose the age restriction as an exclusion criterion and, by doing that, we expected to have a more realistic view of natural evolution in cases not intervened.

In our selected sample, the mean age for group 1 was below that of group 2, as the established criterion for the eruption of molars was immediately an age constraint. Splitting the sample by the age of 11, i.e., by the expected usual age of the exfoliation of the 2pm, had a purpose to possibly identify differences in the biological behavior of a not yet exfoliated tooth and of a retained one. Nevertheless, we must emphasize that our population comprised younger patients than the majority of previous studies, which is a pertinent issue if we assume that the infraocclusion of the mandibular 2pm can be diagnosed since the age of 5 with a peak at 8–9 years,[92] a statement that is inconsistent with our findings, as we found a close to 0 incidence below the age of 11 and a peak in the subgroup of 21–25 years.

A 1.44 times higher frequency of M2P agenesis was found in females, in accordance with another retrospective study,[93] but in conflict with one conducted on an Asian population,[2] possibly reflecting different selection criteria and the different genetic origin of the population.[30] In a Portuguese population of a similar origin, a study on the prevalence of the dental agenesis excluding third molars, conducted in 2005–2009, found a 1.30 times greater prevalence in females.[32] In that study, the total prevalence of M2P agenesis was higher (6.0%) than ours, certainly due to the fact that we also required the presence of the retained 2pm. As back in 2005–2009, digital orthopantomography was not yet at our disposal, despite the temptation to enlarge our sample, that previous sample was not included in this study to avoid bias.

Although this is a cross-sectional study, RR, infraocclusion, width Y, and width X were correlated with age. The occasional high RR values correlated with M2P agenesis are not a surprise and were related to older patients, as resorption is expected to increase with age.[39] As group 2 had the second permanent molar in occlusion, we can extrapolate that only this group was older than 12 years. Consequently, we could compare our results with those in non-syndromic cases, especially with the agenesis of third molars from the same quadrant, which may be found in 48% of patients.[33,48] As a third molar should only be considered as missing after the age of 14, the decision to early extract the retained 2pm may be risky, since space closure can occur with the mesial movement of the posterior tooth sector before it is certain that a third molar is present, leaving open the possibility of the agenesis of third molars, with the consequent absence of a vertical stop for the maxillary second molar.

We found that the age of 10–15 years and 21–25 years were critical phases for the loss of the 2pm. Surviving those phases with favorable occlusal function boosts longevity, which could encourage research in populations far beyond the pediatric age.

Given our results, hypothesis H_1 was accepted, and H_0 was rejected, as we found that the 2pm had the root and occlusal conditions to preserve the space for the corresponding absent M2P for at least 25 years, a finding beneath the interval found by Bjerklin et al. (16–30 years).[28]

Longitudinal randomized clinical trials (RCTS) with the inter-study standardization of the evaluation criteria and well-defined clinical evaluation of the occlusion/function parameters are needed to calculate the real mean longevity of these second primary molars and to support the general dentist, especially when there are no other reasons for carrying out orthodontic treatment.

Limitations

The retrospective design is a limitation of the present study. Nevertheless, the original sample was considerable in terms of size. The population studied originated from the general population and not from orthodontic or pediatric dentistry patients. The selected sample had no age restriction. Another limitation might be that there were more clinical records from female patients than from male patients due to the unbalanced gender ratio in dental clinics. Still, even so, we found a relatively higher prevalence of M2P agenesis with the retained 2pm in females than in males. Working with the data obtained from patients within an age window of 29 years (7–36 years) and a mean age of 16.38 years allowed drifting away from the mean expected period for the exfoliation of the primary molar, which was a positive factor in terms of reducing the possibility of biased results due to individual differences in the exfoliation age.

Clinical considerations

Given the possible extended survival of the second primary molar, well-documented no-intervention treatment must be weighed, mainly in cases without orthodontic issues or with financial constraints, as the second primary molar can survive for a similar or even longer period as compared to a prosthetic option.

Conclusions

There is a good prognosis for the survival of the second primary molar when it remains beyond the average age of its exfoliation in cases of second premolar agenesis. In our study, we showed that it could replace the absent permanent premolar up to 36 years of age (the oldest patient found with both second premolar agenesis and the second primary molar retention).

Mandibular second premolar agenesis occurs with the retention of the mandibular second primary molar beyond the age of 25. If so, it might probably last for a long time, as root resorption decreases after that age.

The loss of space caused by the second primary molar infraocclusion is not a frequent problem, as infraocclusion is not significant in most cases, with higher values found in the oldest adult patients.

Ethics approval and consent to participate

The ethical approval was provided by the Ethics Committee at the University Institute of Health Sciences (IUCS)/CESPU, Gandra, Portugal.

Data availability

All data analyzed during this study is included in this published article.

Consent for publication

Not applicable.

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Systematic Review

Esthetic Perception of Different Clinical Situations of Maxillary Lateral Incisor Agenesis According to Populations with Dental and Non-Dental Backgrounds: A Systematic Review and Meta-Analysis

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Abstract: Treatment of unilateral or bilateral maxillary lateral incisor agenesis is challenging, time-consuming, expensive, and requires careful treatment planning, predictability, and esthetics. This review aimed to identify differences in esthetic perception among orthodontists, general dentists, differentiated dentists, and laypersons, which may interfere with treatment options. EBSCO, PubMed, ScienceDirect, Cochrane Library databases, and Google Scholar were searched using keyword pairing and a Boolean expression, "(congenitally missing OR agenesis OR hypodontia) AND (maxillary lateral incisors) AND (esthetic perception OR smile) AND (laypersons OR dental professional OR general dentist OR orthodontists)." Reviews and case studies were excluded. A total of 13 studies were selected for qualitative analysis (adapted ROBINS-I) and 11 were selected for meta-analysis ($p < 0.05$) after being sub-grouped into "Opening vs. Closure" and "No remodeling vs. Dental remodeling vs. Dental and gingival remodeling" groups. A meta-analysis evaluated the magnitude of the difference between groups based on differences in means and effect sizes ($\alpha = 0.05$; 95% CI; Z-value 1.96), revealing that the esthetic perception of maxillary lateral incisor agenesis treatment remains controversial even among professionals. Gingival remodeling was not valued compared to isolated dental remodeling. Studies lack rigorously comparable methodologies. Discussion with the patient is pertinent in doubtful situations, as the best treatment option remains unclear, and overtreatment should be avoided.

Keywords: maxillary lateral incisor agenesis; esthetic perception; laypersons; general dentist; dental professional; orthodontist

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1. Introduction

Esthetic perception of the smile involves a subjective response to visual sensory stimuli and the ability to recognize and appreciate qualities such as symmetry, balance, proportion, and harmony [1,2]. It is a complex cognitive and emotional process involving both conscious and unconscious parts of the mind and is influenced by factors such as culture, personal experiences, and context, meaning that different individuals may have different esthetic preferences and evaluations [3,4]. A balanced, symmetrical smile is considered essential for facial esthetics, influencing facial expression, overall physical appearance, emotional expression, individual personality, and psychological well-being [5]. Agenesis (developmental absence) of anterior teeth negatively affects interpersonal relationships and self-esteem, leading patients to seek treatment [6–9]. A patient's self-image and expectations play an essential role in clinical treatment decisions [10,11] similar to the esthetic judgment of dentists [12,13].

Maxillary lateral incisor agenesis (MLIA) is the second most frequent kind of non-syndromic congenital tooth agenesis with a 1–2% prevalence in the Caucasian population, being bilateral in more than half of cases, and if unilateral, frequently is associated with peg-shaped laterals on the contralateral side [6,14–17].

Treating unilateral or bilateral MLIA is challenging, involving space opening (SOP) with subsequent prosthetic replacement of the missing lateral incisor or space closure (SCR) by moving the canine into the edentulous space followed by tooth remodeling (porcelain crown or resin-matrix composite restorations) for a complete tooth match with the contralateral incisor [6,7,9,14,16,18,19]. Both treatment options are expensive, time-consuming, complex, and controversial [16,20–23], but unless extractions are made, no significant differences exist between them concerning the time spent in treatment [24].

SCR often requires remodeling of the canine into a lateral incisor and of the first premolar into a canine to match the anatomy, color, and gingival contour of a naturally erupted tooth [6,7,16,25]. A post-treatment periodontal evaluation over a period from 6 months to 7 years found no significant differences in plaque index and bleeding index between the SCR and SOP groups [26], in contradiction with findings from other cohorts wherein SCR patients possessed better periodontal health after 5 years post-treatment [22,27]. A thick periodontal biotype was associated with the SOP group, and the thin biotype was associated with the SCR and control groups [26]. Patients with MLIA treated with space closure, first premolar intrusion, and canine extrusion were found periodontally healthy 10 years after treatment with a periodontal status comparable with the condition of patients without MLIA who have received similar orthodontic treatment [28].

Concerns to take into account include the possibility of root resorptions in cases involving orthodontic treatment [11] and the level of gingival exposure during smiles in cases involving lateral incisor substitutions with an implant-supported crown [29]. Despite the absolute position of the gingival zeniths, clinical situations treated with implants show values relative to the reference line, similar to those of aligned teeth without lateral incisor agenesis [30,31].

Perception and esthetic-judgment studies can help dental professionals understand how laypersons evaluate all the details concerning their smiles and those of others and prioritize patients' needs to avoid biased professional evaluations [7,8,22,32]. Concerning the esthetic perception, compared to general dentists and orthodontists, laypersons tend to accept a larger scale of smile deviations, such as midline deviation up to 2.2 mm, exposed gingival margins while smiling, and variation in tooth coronal morphology [8,16,33,34], perhaps because laypersons observe the eyes in the images before attending the mouth [35].

Esthetic results play an essential role in managing the clinical situation of MLIA, and general dentists and orthodontists tend to overestimate their importance more than their functional aspects [16]. However, each professional has a fickle opinion when asked to choose the best treatment to follow (closure or space opening) or about the esthetic result obtained in cases already treated [36], and the education levels of professionals' dental backgrounds also seem to play a role [4,37]. Back in 1976, Senty [38] said that the "diagnostic decision to open or close the space is always a compromise" and that one simple question is to be answered: "Which is the best compromise for the patient taking an interest both functional and esthetic?"

Since then, despite evolution in technological and professional technical quality, doubts persist [39], mainly when treating young patients, especially in unilateral situations of MLIA, as subjects treated with implant-supported crowns will have inevitable long-term infraocclusion of the replaced lateral incisors [27] or will experience the need for periodic maintenance if treated with conservative restorative techniques [20,27,39–41].

A systematic review to elucidate the esthetic perception of laypersons, general dentists, and orthodontists in MLIA clinical situations may help evidence-based treatment decisions, especially in doubtful clinical situations in which any treatment option is valid.

The primary aim of this systematic review was to clarify the differences in esthetic perception between populations with dental or non-dental backgrounds and to compare the esthetic perception of MLIA situations treated with space closure with those treated with space opening. In space-closure situations, determining the esthetic impact of dental and gingival remodeling of the mesialized canine, with or without symmetry, was also considered pertinent. The authors hypothesized that esthetic perception would be the same among all observers when evaluating the treated clinical situations of MLIA.

2. Materials and Methods

2.1. General Aspects

The review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 recommendations [42]. The population, intervention, comparison, and outcome (PICO) question was: "Which of the treatment options, closure or space opening, whether MLIA is unilateral or bilateral, is perceived as more esthetic by different populations?" The clinical situation of the treated MLIA constituted the study population. The treatment option was intervention, specifically the closure or opening of the space. A comparison was made between unilateral and bilateral situations, and between canine approaches performed by the dentist. The outcome was esthetic scoring by observers (laypersons, patients, general dentists, orthodontists, and other dental professionals).

2.2. Search Strategy and Criteria

Electronic databases (EBSCO, Medline/PubMed, ScienceDirect, and Cochrane) and the search engine Google Scholar were searched from 1 January 2000 to 31 July 2022 by pairing the keywords congenitally missing, maxillary incisors lateral, anterior tooth agenesis, agenesis, hypodontia, esthetic, aesthetic, perception, smile, laypersons, dentist general, dental professional, orthodontists, and by the Boolean expression: "(congenitally missing OR agenesis OR hypodontia) AND (maxillary lateral incisors) AND (esthetic perception OR smile) AND (laypersons OR dental professional OR general dentist OR orthodontists)." Articles written in languages other than English or Portuguese, literature or systematic review articles, and case studies were excluded. To frame the universe of publications related to the theme and validate the chosen Boolean expression, an open search independently combining keywords was performed in previous databases and the Google Scholar search engine [43] followed by filtering within the methodology.

Three investigators (M.J.C.L., M.C.L. and T.P.) discussed the search strategy. Articles identified via the search strategy, following the exclusion criteria, and once-set concordant standards were independently selected by two researchers (M.J.C.L. and M.C.L.) after removing duplicates. Publications and titles were analyzed followed by abstract reading and a complete analysis of the selected articles. The references in the selected papers were subjected to a detailed search for potentially relevant articles.

2.3. Data Extraction and Collection

Data on the esthetic perceptions of professionals or laypersons, types of treatment, and symmetries of procedures were extracted from the selected studies and organized in tables. Disagreements between the reviewers in these two stages were resolved by consensus with a third researcher (T.P.).

To better understand and interpret the results and methodologies, the authors formed a group comparing procedures involving opening the space to procedures involving the closure of the space ("Opening vs. Closure") and another within the space-closure group that compared the type of canine approach performed by the dentist ("Canine without remodeling vs. Canine with dental remodeling vs. Canine with dental and gingival remodeling"). For convenience and comparison, the scale of 0–100 mm was converted to a 0–10 scale. Mean conversion with a 95% confidence interval ($p < 0.05$) was performed to standardize the results of different studies using a previously described methodology [44,45]. The sample size for each study is presented in a short table.

2.4. Methodological Quality

An adapted methodological quality analysis using seven items based on the risk of bias in non-randomized studies of interventions (ROBINS-I) [46] assessed the risk of bias in the selected studies. Parameters considered essential for risk of bias assessment were adapted as previously described in other dentistry studies [47]. The sample size calculation, accurate description of the sample, occurrence of dropouts, use of valid methods, presence of confounding variables, blind measurements, proper statistical analysis, and final overall assessment of the articles were used. Each study was scored as High (5–7), Moderate (3–4), or Low (0–2) quality.

The sample-size calculation established the number of individuals included to obtain valid conclusions. A sample description was considered correct if the origin and main features of the sample were described and if the degree of professional specialization was described in those cases involving health professionals. The presence of dropouts was a missing item because the participants were voluntarily committed to responding to the survey after visualizing the clinical situations presented and were not involved in studying the technique. The employed method was evaluated using valid method parameters. The presence of confounding variables analyzed aspects related to the model used, which could confuse or abstract participants from the crucial study details.

The "blind measurement" parameter implies the unknowledge of the cases to be assessed for qualitative or quantitative evaluations, avoiding the usurpation of opinions. Correct descriptive and inferential statistics were analyzed using appropriate statistical analysis parameters.

2.5. Meta-Analysis

A meta-analysis focusing on the esthetic evaluations of treatment options according to the observers was conducted using a software program (Stata v17.0; StataCorp, Lakeway, TX, USA). Subgroup analyses were conducted according to author, type of treatment, unilateral or bilateral MLIA, and type of recontouring (canine or gingival interventions).

Statistical heterogeneity was determined using the I^2 test ($\alpha = 0.05$). A random-effects meta-analysis model with restricted maximum likelihood was used to compare the means across all studies ($p < 0.05$). Subgroups with studies that provided control images were formed to determine intra- and inter-study heterogeneity after calculating the difference between means and effect sizes ($\alpha = 0.05$; 95% CI; Z-value 1.96). The Hedge's g statistic was preferred to be more adequate for small samples and significantly different sample sizes. Funnel and Galbraith plots were used to assess publication bias (random-effects model; $\alpha = 0.05$; 95% CI; Z-value 1.96) and heterogeneity (random-effects model; $\alpha = 0.05$; 95% CI; Z-value 1.96). A paired *t*-test ($p < 0.05$; 95% CI) was run for subgroups to determine whether there was a statistically significant mean difference between the initial image and the remodulation image after analyzing data for normality (Shapiro–Wilk test of normality, $p < 0.05$; 95% CI) and the identification of significant outliers (boxplot, $p < 0.05$; 95% CI), assuming that the variables were continuous and the groups were related. In the absence of a control image, data obtained for the "No remodeling" group were considered control references for comparison with the "Dental remodeling" or "Dental and gingival remodeling" groups.

Two studies selected for data analysis were not plotted because one [6] reported a qualitative rating, and the other [19] did not rate the images independently but as a synoptic global evaluation, not distinguishing bilateral from unilateral situations, and using a numerical scale impossible to convert for quantitative analysis.

3. Results

3.1. Study Selection

The search of the different databases with a Boolean expression and after duplicate removal retrieved 36 articles, of which 6 were excluded due to their titles, 10 were excluded due to their abstracts, and 7 were excluded after integral reading revealed that they failed to meet the set objectives or were not related to MLIA. Finally, one [48] was added through a manual search. A total of 13 studies [6,7,9,14,16,18,19,25,48–52] were included in the qualitative analysis.

The broad search strategy using keyword pairing retrieved 2787 titles. After duplicate removal and post-search filter application (language, type of publication, study objectives, and no-MLIA), the same studies attained through the Boolean search remained, including the one that was manually introduced. The selection strategy is illustrated in Figure 1.

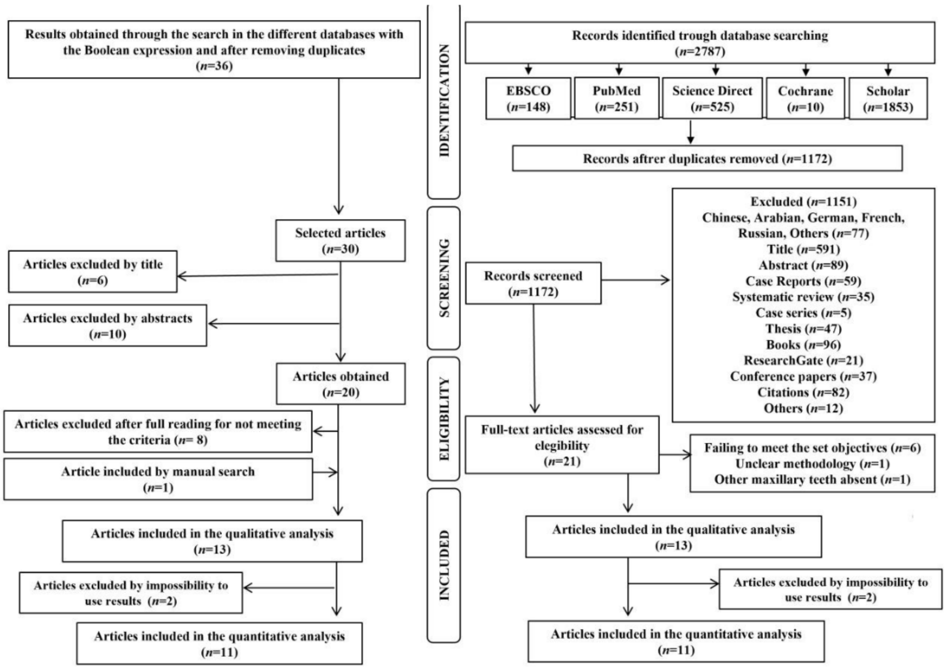


Figure 1. Synopsis of the PRISMA strategy for focused and broad article selection. (EBSCO, EBSCO-Information Services, library database services (electronic databases, e-books, and other library resources); PUBMED, free web search engine; accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics; Scholar, Google Scholar, free web search engine, index of full text or metadata of scholarly literature across an array of publishing formats and disciplines).

3.2. Study Characteristics and Descriptive Data Analysis

The methodological quality analysis is summarized in Table 1.

Only three studies [9,14,16] used sample size calculations to confirm the inclusion of sufficient individuals to represent the population. Concerning the correct sample description, globally, there was a lack of distinction between general dentists and specialists, namely orthodontists, not always well-defining their professional training and not being, in some cases, officially considered specialists [16,18,19,48,52]. The digital model [14,16,48] and the real model [6,7,9,18,19,25,49–52] were considered valid for meeting the goals proposed by the authors.

Table 1. Synthesis of qualitative analysis for risk-of-bias assessment.

	Sample Size Calculation	Selection Description	Dropout	Valid methodology	Confounding Variables	Blind Measurements	Adequate Statistics Analysis	Qualitative Scoring
Armbruster et al. 2005 [19]	-	?	+	+	-	+	+	Moderate
Brough et al. 2010 [6]	-	+	+	+	+	+	+	High
De-Marchi et al. 2014 [7]	-	?	+	+	-	+	+	Moderate
Gomes & Pinho 2019 [25]	-	+	+	+	+	+	+	High
Li et al. 2019 [48]	-	?	+	+	+	+	+	High
Mota & Pinho 2016 [14]	+	+	+	+	+	+	+	High
Pinho et al. 2015 [18]	-	?	+	+	+	-	+	Moderate
Qadri et al. 2016 [49]	+	+	+	+	+	-	+	High
Rayner et al. 2015 [9]	+	+	+	+	+	+	+	High
Rosa et al. 2013 [16]	+	?	+	+	+	+	+	High
Schneider et al. 2016 [50]	-	?	+	+	-	+	+	Moderate
Souza et al. 2018 [51]	+	+	+	+	+	+	+	High
Thierens et al. 2017 [52]	-	+	+	+	+	+	+	High

(+)—Item with quality; (?)—Item with dubious quality; (-)—Item without quality; Scored by number of (+) as High (5–7), Moderate (3–4), or Low (0–2) quality.

Blind measurements were specified in only one study [19]. The item “opening vs. closure” was present in three studies [18,49,50] comparing bilateral opening with bilateral closure and one study [7] comparing unilateral opening with bilateral closure (with dental remodeling). In the space-closure group, data to distinguish unilateral from bilateral situations from nine studies [7,9,14,16,18,25,48,51,52] were registered along with data from a comparison of canines without remodeling, with dental remodeling only, or canines with dental and gingival remodeling.

The results of the analyzed studies were acquired, presented, and grouped based on different classification scales. In most cases, participants performed both quantitative and qualitative evaluations. Numerical ranges were found from 0 to 10 ((1)-less attractive and (10)-more attractive) and from 0 to 100 mm (VAS analogic scale) ((0–50.99 mm) -unpleasant and (>51 mm)-pleasant). Studies using the 0–100 mm scale showed greater dispersion values, unlike those using the 0–10 scale, assuming only whole numbers.

Table 2 shows the sample size found in the analyzed studies, revealing heterogeneous observers in terms of type and number.

Table 2. Sample sizes according to author and observer.

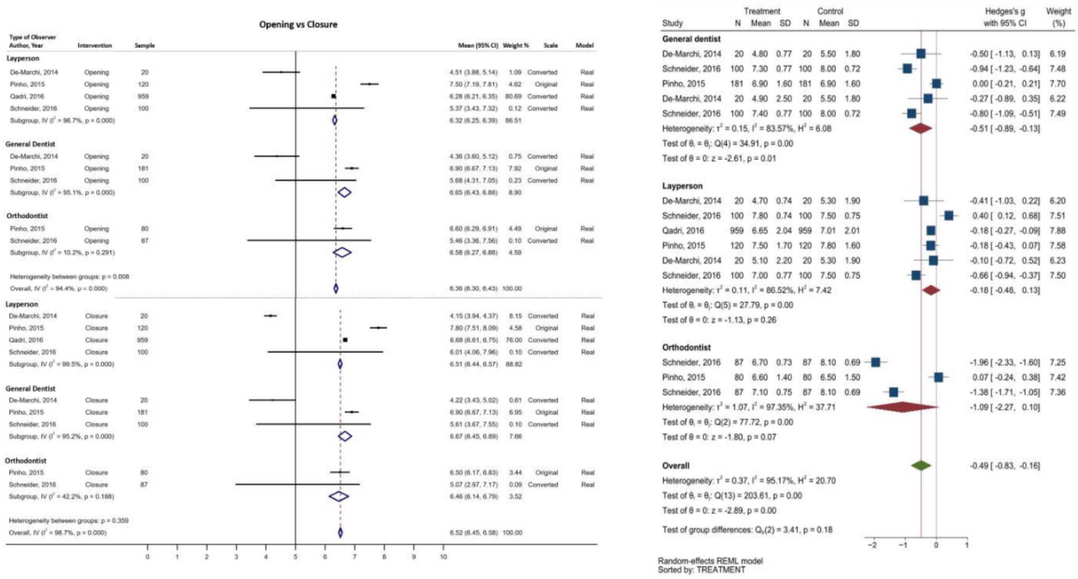
Author, Year	Type of Observer	Sample
Armbruster et al. (2005) [19]	General dentist	140
	Layperson	60
	Orthodontist	40
	Dental specialists	29
Brough et al. (2010) [6]	General dentist	40
	Layperson	40
	Orthodontist	40
De-Marchi et al. (2014) [7]	Orthodontist	20
	Periodontists	20
Gomes and Pinho (2016) [25]	General dentist	141
	Layperson	142
	Orthodontist	100
	Periodontists	51
Li et al. (2019) [48]	Layperson	60
	Orthodontist	41
Mota and Pinho (2016) [14]	General dentist	215
	Layperson	303
	Orthodontist	81
	Prosthodontist	55
Pinho et al. (2015) [18]	General dentist	181
	Layperson	120
	Orthodontist	80
Qadri et al. (2016) [49]	Layperson	959
Rayner et al. (2015) [9]	General dentist	30
	Layperson	30
	Orthodontist	30
Rosa et al. (2013) [16]	General dentist	40
	Layperson	40
	Orthodontist	40
	Patient	40
Schneider et al. (2016) [50]	General dentist	100
	Orthodontist	87
Souza et al. (2018) [51]	Dental student	50
	Dental surgeon	50
	Layperson	50
Thierens et al. (2017) [52]	General dentist	77
	Layperson	46
	Orthodontist	37
	Periodontists	14

Table 3 presents the data extracted from the selected studies. The 13 studies submitted for quality analysis were non-randomized, and 5 studies [6,16,18,48,49] did not include control images.

The two studies that are not plotted are briefly summarized here, considering their relevance to a broader discussion. The first study [6] compared the attractiveness of smiles between patients with MLIA and those with complete natural dentition. In general, maxillary canine morphology was perceived by orthodontists, dentists, and laypersons. Broad canines were classified as unattractive, and narrower canines were classified as more attractive in all groups. Sharp canines were rated negatively by all the groups. The second study [19] compared the esthetic attractiveness of adhesive Maryland bridges, implant-supported crowns, canine mesialization, and natural dentition without MLIA, based on a series of dental photographs from MLIA clinical situations. There was no agreement among the dental professional groups or between these groups and laypersons regarding the best score for space closure with canine mesialization. Implant-supported crown substitution after space opening had the highest score, indicating less attractiveness, as higher scores reflected a less-favorable evaluation (best score (7) and worst score (35)). Assessments of symmetrical and asymmetrical clinical situations were combined, making it impossible to obtain references to the influence of symmetry or asymmetry on smile perception.

3.3. Meta-Analysis

A comparative analysis of the data collected from the 11 studies available for quantitative analysis is shown in Figures 2–4. Data on the calculation of the difference in means and effect size (α = 0.05; 95% CI; Z-value 1.96) are presented in Supplementary Table S1. Forest plots with differences in means, by author and (a) type of remodeling, (b) type of agenesis, and (c) observer can be found in Supplementary Figure S1a–c.



(**a**) (**b**)

Figure 2. Forest plots summarizing results of group "Opening vs. Closure." (**a**) Comparison according to author and observer. (**b**) Difference in means with Hedges's g effect between control and intervention groups with data obtained from the included studies [7,18,49,50].

Table 3. Data extracted and collected for qualitative analysis from the studies included in the present systematic review (population, intervention, objectives, outcome, validity of the methodology, confounding variables, and study design).

Study	Population	Interventions	Objectives	Parameters	Outcome	Validity of Methods	Confounding Variables	Study Design
Armbruster et al. (2005) [19]	40 (L) 140 (GDPs) 43 (O) 29 specialists (SP) (9 PT, 11 END, 3 SUR, 4 OD, and 2 P)	Direct visual observation. Observers blinded for treatment options.	Esthetic appearance of various treatment options of treated MLIA cases.	MLIA treated with Maryland bridges (MB), dental implants (IP), orthodontic canine reposition (CR), or no-MLIA (control)(NT). 1 (more) to 5 (less attractive).	(O) NT > CR > MB > I (GDPs)-NT = CR > MB = I (SP)-NT = CR > MB = I (L)–CR > NT > MB > I ($p < 0.001$).	YES real model	YES multiple variables	N-RCT CI
Brough et al. (2010) [6]	40 (L) 40 (GDPs) 40 (O)	Direct visual ranking of images digitally manipulated from original photography. Blind and random evaluation.	Smile attractiveness in patients with MLIA vs. natural whole dentition.	Gradual increment of canine width, crown height and morphology, and gingival margin height. No quantitative measures.	(All) Dark, large canines, gingival margin >0.5 mm above central incisive-unattractive. Narrow canines–better rank. (GDPs)-natural tones; (O)-slightly brighter tones. (L)-brighter tones; (O)-cusps < 1.0 mm; (L)-cusps 1.0–1.5 mm. (Male GDPs)-most critical	YES digital model	NO same teeth same gum	N-RCT NCI
De-Marchi et al. (2014) [7]	20 (L) (10M,10F) and 20 (GDPs) > 4 years practice (10M,10F)	Direct visual observation of 68 photographs 26 (SC + R) 20 (SO + IP) 22 (no-MLIA).	Attractiveness of smiles in patients with MLIA vs. natural whole dentition.	Controlled photographic protocol. Unpleasant: 0 to 50.99 mm. Nice: 51–100 mm	Volunteers -control group–very pleased with their smiles. Patient satisfaction SC +R > SOI; more satisfied than control group ($p < 0.002$). Pretreatment image-least esthetic. Orthodontic treatment-improvement.	YES real model	YES different lips different teeth	N-RCT CI
Gomes & Pinho (2019) [25]	142 (L) 141 (GDPs) 100 (O) 51 (PT)	Quiz. Numerical Valuation. Ranking in ascending order. Anonymous.	Esthetic perception of asymmetric MLIA treated with SC and canine mesialization.	Space closure of MLIA with asymmetric canines. 2 symmetric simulations. Digital manipulation (smile 1—smaller canines) (smile 2—larger canines). Visual analog scale (VAS) (0–10).	Symmetric canines–most esthetic. Larger canines–more esthetic. Differences between (GDPs and L) regarding the most and least esthetic approach($p < 0.05$). (L) more impressed than professionals; dental specialists more demanding ($p < 0.05$).	YES real model	NO same parameters same model	N-RTC NC

Table 3. *Cont.*

Study	Population	Interventions	Objectives	Parameters	Outcome	Validity of Methods	Confounding Variables	Study Design
Li et al. (2019) [48]	60 (L) 41 (O)	Direct visual photo observation. Ranking of images digitally manipulated from original photography. 140	Canine edge width and height affect in dental esthetics in canine mesialization.	127 closure treatments. Top 5 most pleasant cases, digitally manipulated; 140 images with canine edge widths ((0, 12.5, 25, 37.5, 50, 62.5 and 75% of the central incisor width) and heights (−0.5, 0, 0.5 and 1.0 mm relative to central incisor edge)).	Most esthetic canine shape-canine edge-62.5% of the central incisor width and −0.5 mm gingival to the central incisor edge ($p < 0.005$). Canine edge width ($p = 0.003$) and height ($p < 0.001$) affect esthetics in canine substitutions.	YES Digital model	NO same gingiva same teeth	N-RTC NCI
Mota & Pinho (2016) [14]	303 (L) 215 (GDPs) 81 (O) 55 (PT)	Online survey. Digital manipulation.	Perception of smile attractiveness in MLIA cases treated with canine mesialization.	9 digital photos of MLIA treatment involving space closure. Unilateral and bilateral. Numeric scale (1–10) (least to most attractive) >5-attractive <5-unattractive.	(L)-better scored all cases/other groups. (All)–ideal smile = smile with lateral incisors. (All)–canine remodeling-more attractive. GDPs/O/PT- favor canine remodeling + gingival remodeling. All photos score- O < GDPs < L.	YES digital model	NO	N-RCT CI
Pinho et al. (2015) [18]	120 (L) 181 (GDPs) 80 (O)	Online survey. Esthetic perception preferences. Pre-and post-treatment evaluations.	Smile esthetic perception in patients with MLIA with respect to gingival exposure.	4 clinical cases. 24 smile photos. Numerical scale 0–10.	Males- highest scores. Symmetric cases and medium smile- higher scored. Gingival exposure-significant influence on the esthetic perception in post-treatment cases ($p < 0.001$).	YES real model	YES same lips different teeth	N-RCT NCI
Qadri et al. (2016) [49]	959 (DSt) and University staff F/M (76%/24%) 5 (O) 5 (RD)	Online survey. 959 completed responses with 9590 judgments. 4 pairs of photos. BILATERAL	Esthetic perception concerning the outcome of bilateral MLIA treatment patients with SC, SO, or IP.	21 patients (11 SC/10 PR). 10 specialist dentists (O + RD) ranked the photos. Most attractive (1)-least attractive (22). Only bilaterally MLIA included in this study.	SC-more attractive/PR ($p < 0.001$). Females and staff-higher ratings. Females/males-preferred SC/PR = 3/1 ($p < 0.001$). Space closure more attractive than space opening by (L).	YES Real morphed model Photo size standardization	YES multiple variables	N-RCT NCI Cross-sectional

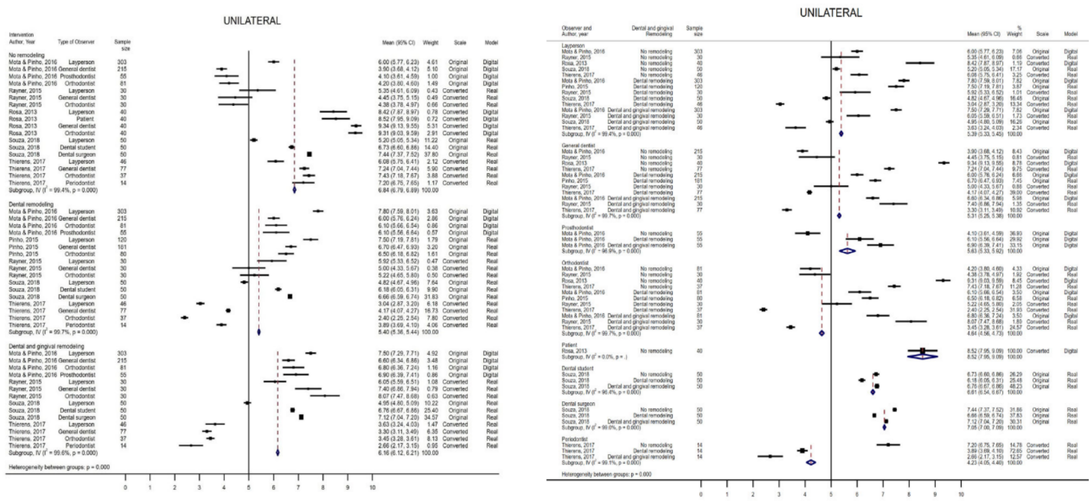
Table 3. *Cont.*

Study	Population	Interventions	Objectives	Parameters	Outcome	Validity of Methods	Confounding Variables	Study Design
Rayner et al. (2015) [9]	30 (L) 30 (GDPs) 30 (O)	Direct visual observation. Digital manipulation. (average female face image based on frontal photos of 4 female volunteers).	Effect of canine characteristics and symmetry on perceived smile attractiveness, in MLIA treated with canine mesialization.	1 ideal image. 6 morphed images (canine with lateral incisor-unilateral and bilateral). 3 types of canine created using software. Variations in shape, length, and color.	(O, GDPs)-space closure with canine significantly less attractive/ideal smile unless replaced by ideal canines($p < 0.001$). (L)-lateral incisors replaced with canines different from ideal smile, but not clinically significant. (All)– unilateral replacement not significantly less attractive than bilateral replacement.	YES real model	NO same face same teeth same smile	N-RCT CI
Rosa et al. (2013) [16]	40 (L) 40 (OP) 40 (GDPs) 40 (O)	Quiz. Digital model of an ideal smile. Ranking (descriptive analysis). Numerical valuation.	Valuation of esthetic perception in altered smiles due to MLIA with or without treatment.	12 simulations. Visual analog scale (VAS) 0 to 100.	Significant differences–(All professionals) and (L) ($p < 0.005$). Orthodontic treatment, absence of diastema, symmetry-higher valued by all groups.	YES digital model	NO same parameters same model	N-RCT NCI
Schneider et al. (2016) [50]	100 (L) 100 (GDPs) 87 (O) Blinded observers	Direct visual photo observation. 9 frontal photos 3-SC + R 3-SO + IP 3-no-MLIA	Esthetic evaluation of implants vs canine substitution in patients with MLIA.	7 pairs of bipolar adjectives. Smiles classified from 1–5 (less-more attractive).	O/GDPs-no-MLIA more attractive than SC + R > SO + IP (Non-significant). L-SC + R > no-MLIA > SP + IP. L/GDPs-Better scores for SC + R. All groups-Worst scores for SO + IP (Nonsignificant).	YES Real Model Best photo preselection by orthodontists	YES multiple variables Mixed cases	N-RCT CI

Table 3. *Cont.*

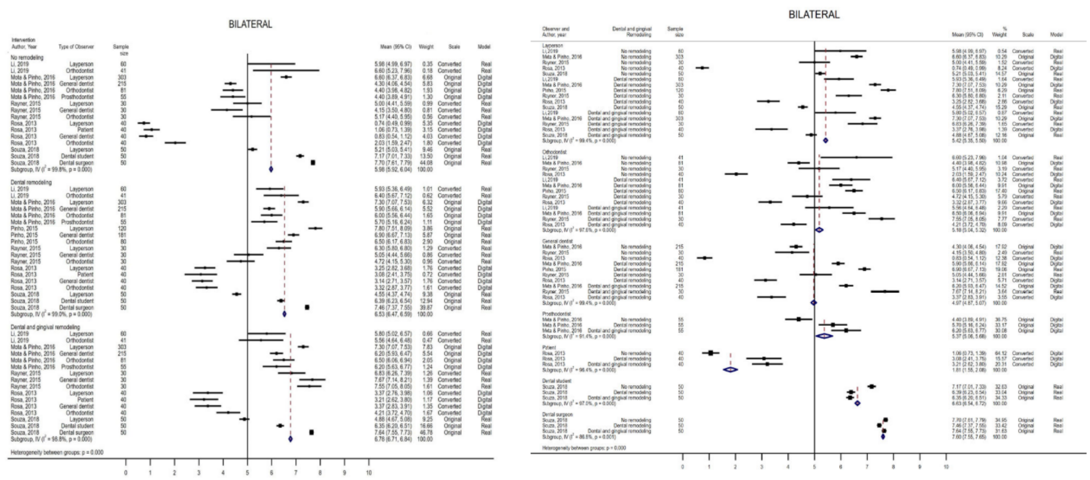
Study	Population	Interventions	Objectives	Parameters	Outcome	Validity of Methods	Confounding Variables	Study Design
Souza et al. (2018) [51]	(L) (GDPs) (DSt) 150 (22 and 40 y) Similar socioeconomic status	Direct visual observation. Digital manipulation. SC UNILATERAL BILATERAL (R + G) (R + B + G) ® (R + C + G) (R + B)	Perception of the attractiveness of MLIA replaced with canine mesialization.	Extraoral photograph. 20-year-old woman-normal occlusion. Software manipulation of original photograph. Mandibular arch without modifications. Various compositions with different sizes and proportions of height and width of the teeth to simulate repositioning of the canine on the left, right, or both sides. VAS 0 to 10, (less to more esthetic).	Original image–highest acceptance by (All). Lowest acceptance–left side alterations. Bilateral R + G-highest scores from (L). R + C-lowest score from (GDPs). (DSt)-least attractive–bilateral alterations Globally–(L)-lowest scores/other groups Least acceptable–(All) groups-bleaching (L)-attractive—bleached mesialized canines without treatment. (GDPs and DSt)- notice more differences than (L). (L)-cannot detect some interventions.	YES Real Digitally manipulated Model	NO same teeth same gum same mandibular teeth	N-RCT CI
Thierens et al. (2017) [52]	46 (L) 77 (GDPs) 37 (O) 14 (P) (age, experience, and gender, except the mean age of (O) to (L)) Female: Male (ratio 1.5:1)	Direct visual observation. Digital manipulation. Ranking by attractiveness. UNILATERAL	Size, morphology, and color of the substitute canine influence on dento-gingival attractiveness perceived by dental professionals and laypeople.	Standard image. Five series (width, color, gingival margin height, canine crown tip, and gingival margin height of the neighboring first premolar). Image most deviated from the standard/each parameter combined into a final series.	Dark canine and pronounced tip of a substituted canine-most unattractive to (All) professionals and (L). Gingival height of the neighboring premolar-least unattractive–(All) groups of examiners.	YES Real Digitally manipulated model	NO same teeth same gum same mandibular teeth	N-RCT CI

All-all groups of observers; B-bleaching; CI-control image; MLIA-maxillary lateral incisor agenesis; F-female; L-layperson; G-gingival recontouring; GDPs-general dental professional; M-male; NCI-no control image; N-RCT-non-randomized controlled trial; O-orthodontist; M-male; PT-prosthodontist; R-reshaping of the canine crown; SC + R-space closure and composite restorations; and SO + I-space opening + implant-supported crown.



(**a**) (**b**)

Figure 3. Forest plot summarizing results obtained in group “No remodeling vs. dental remodeling vs. dental and gingival remodeling”, UNILATERAL. (**a**) Comparison according to type of remodeling by the same author. (**b**) Comparison according to observer and type of remodeling, with data obtained from the included studies [9,14,16,18,51].



(**a**) (**b**)

Figure 4. Forest plot summarizing results obtained in group “Canine without remodeling vs. Canine with dental remodeling vs. Canine with dental and gingival remodeling”, BILATERAL. (**a**) Comparison according to type of remodeling by the same author. (**b**) Comparison according to observer and type of remodeling, with data obtained from the included studies [9,14,16,18,48,51].

When comparing opening and closure (Figure 2a), the data showed no significant differences ($p < 0.05$) between the two treatment types in the four studies analyzed [7,18,49,50]. These forest plots highlight the relatively low scores observed for both treatment options in the study by De-Marchi et al. [7], a high dispersion of values in the study by Schneider et al. [50], and a trend toward higher scores according to laypersons compared to dental professionals in the study by Pinho et al. [18]. The study by Qadri et al. [49], which had the largest sample, showed no difference between opening or space closure for the same observer type.

When analyzing the difference in means and effect size ($\alpha = 0.05$; 95% CI; Z-value 1.96) (Figure 2b), the magnitude of the overall effect was medium ($g = 0.5$; $p < 0.05$) for the intervention with larger variations occurring in the study by Schneider et al. [50] in values according to orthodontists.

Overall, in unilateral MLIA, as shown in Figure 3a,b, there was a slight decrease in the scoring of smiles between no remodeling and dental and gingival remodeling. When comparing results within the same article, the study by Rayner et al. [9] showed an increase in rating with increased canine reshaping in all categories of participants, wherein laypersons presented higher assessments than those of professionals, except for dental and gingival remodeling, wherein professionals considered this kind of procedure far more esthetic. Mota and Pinho [14] presented a more significant score increase between the canine without remodeling and the canine with dental remodeling, and the lowest increase for the canine with the two types of remodeling ($p < 0.05$). In this study, the scoring from laypersons was higher than that of professionals for all types of remodeling, appearing less pronounced for complete remodeling ($p < 0.05$). Souza et al. [51] showed a tendency for worse scores for dental remodeling only compared to other interventions in all groups of observers with laypersons presenting the lowest values.

By analyzing the studies that included only one type of procedure, Rosa et al. [16] revealed lower esthetic results in all groups of participants in the case of canines without remodeling, whereas Pinho et al. [18] (canines with dental remodeling) found values similar to those of other studies using the same procedure. Data from Thierens et al. [52] showed lower scores for dental only or dental and gingival remodeling compared to no remodeling and high heterogeneity among groups of observers.

If the MLIA was bilateral (Figure 4a,b) with symmetry of the smile, there was no significant discrepancy in esthetic appreciation ($p < 0.05$); however, there was a more positive assessment regarding the groups with dental and gingival remodeling. As an exception, the study by Rosa et al. [16] showed a negative appreciation for all types of remodeling according to all observers.

When comparing the different types of procedures within each article, in the study by Rayner et al. [9], unlike what happens for other therapeutic options, laypersons grant the lowest value for gingival remodeling, as in the study by Rosa et al. [16].

Pinho et al. [18] obtained results with a distribution similar to that of Mota and Pinho [14]. In the last study, it was possible to observe a higher appreciation in the laypersons group than in the others. However, this difference was less marked in cases with tooth and gingival remodeling owing to a better ranking from dental professionals.

Regarding the sample used in each of the 11 studies suitable for the meta-analysis, as shown in Table 2, there was a disparity that may have induced an overestimation of the intervention effect, as suggested by the asymmetries shown in Figure 5a–f, and some amount of bias is possible. Two studies [16,52] had more publication bias than the other studies.

In Figure 6, heterogeneity among the effect sizes of the studies is suggested because several studies were outside the 95% CI region. Some studies, located toward the right of the x-axis, reported high precision. All studies were positioned on or above the green line, and the red line slopes slightly upward, indicating that the intervention is slightly more favorable than the control group.

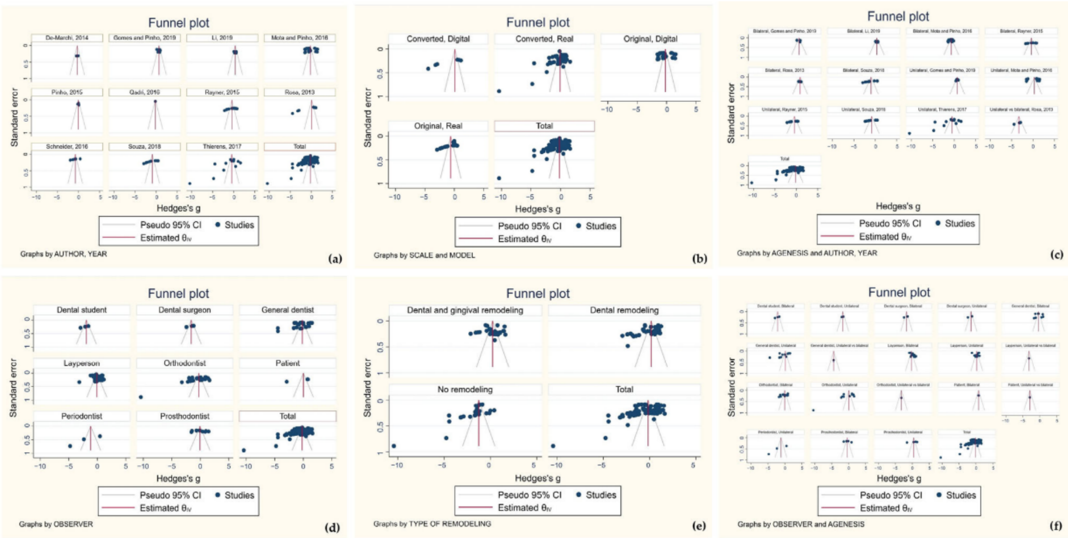


Figure 5. Funnel plot of publication bias by (**a**) author, (**b**) scale and model, (**c**) type of agenesis and author, (**d**) observer, (**e**) type of remodeling, and (**f**) observer and type of agenesis [7,9,14,16,18,25,48,50–52].

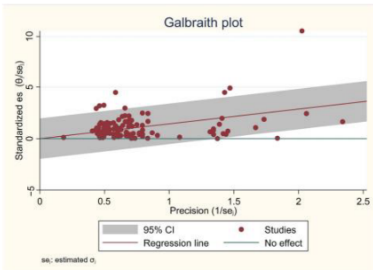


Figure 6. Heterogeneity assessment of effect sizes.

In the paired *t*-test run on the type of treatment subgroup (space opening versus space closure) (Supplementary Table S2), the ideal image (6.93 $\pm$ 1.11) was valued more than the intervention (6.46 $\pm$ 1.09) with a significant decrease of 0.47 (95% CI, 0.7246 to 0.2126) $t(13) = -3.99541$, $p < 0.002$), which in this particular case revealed no preference for any type of treatment.

A paired *t*-test was performed on the type of remodeling subgroups (canine without remodeling, canine with dental remodeling, and canine with dental and gingival remodeling). Supplementary Table S3 showed no significant differences except for the subgroup "canine without remodeling" with the control image (ideal smile) (6.81 $\pm$ 1.29) being more valued than the no-remodeling image (4.47 $\pm$ 1.51) with a significant decrease of 2.34 (95% CI, 3.2270 to 1.4587), $t(13) = -5.7245$, $p < 0.002$), suggesting the need for remodeling in cases treated with space closure.

The results of the Shapiro–Wilk test of normality ($\alpha = 0.05$; 95% CI) and boxplots for the identification of significant outliers ($p < 0.05$; 95% CI) enabled a valid paired *t*-test run (Supplementary Table S4 and Supplementary Figure S2).

4. Discussion

This review assessed the differences in esthetic perception between laypersons and dental professionals (those with specialized skills).

In light of the data obtained ($p < 0.05$), the null hypothesis that no differences existed among observers' esthetic perceptions in different clinical situations of MLIA treatment was rejected.

The authors followed a double strategy to include as many studies as possible. The search with the Boolean expression quickly limited the articles; the broad search validated the first, certifying that no research article was missing. Google Scholar is a free, easily accessible, and growing search engine and despite being more recent has the power to extract similar results [43] as other resources frequently used and reputable (Web of Science and Scopus). This strategy also provides insights into the scientific community's interest in the subject. Nevertheless, despite its accuracy, it has few filters that retrieve a tremendous number of results, thereby producing a large amount of noisy data while searching.

Globally, in the studies found, esthetic analysis does not follow standardized parameters as some studies [14,49,51] have considered both the sizes and characteristics of samples, whereas others [9,16] have considered only sizes. Both calculations were assessed during the methodological rating (Table 1), bearing in mind that the analysis of the first calculations [14,49,51] was more complete. Only five studies [9,14,16,49,51] performed sample size calculations. In one study [19] the authors admitted the lack of sample size calculation as a limitation, as the sample could not represent the entire population, assuming some bias. Two studies [11,53] were excluded for non-discrimination of the agenesis location or target population, single observer evaluation, or non-maxillary agenesis.

4.1. Differentiation Degree among Professionals

The studies did not accurately differentiate each professional category, mainly orthodontists, as official specialization is still being implemented in many countries. An orthodontist can be a professional with clinical experience in orthodontics but with unofficial training. Therefore, a sharp distinction between them and general dentists is lacking, possibly biasing the results. Orthodontists were absent in three studies [7,49,51] or included without specifying their specific training [16,18,19,25,48,50,52], whether they were orthodontic specialists or equivalents [9], or whether the designation extended to senior specialty students and hospital consultants [6]. Only one study [14] described orthodontists as professionals with at least 2 years of full-time training in orthodontics and more than 50% of their clinical practice in the area. Assuming that an orthodontist should be responsible for the treatment plan and decision to open or close the MLIA space, and that orthodontic procedures are often needed before gingival remodeling in situations of space closure, it is important to better differentiate these professionals in future studies. As the treatment should be multidisciplinary, some authors [14,49,52] included restorative dentists, periodontologists, or prosthodontists in their evaluations without specifying their expertise levels.

4.2. Age and Gender of the Participating Population

Regarding the participating population, only two studies grouped the population according to age (25–60 years [16] and a mean age of 25 years [49]), which is a relevant factor [54], as older groups of laypeople tolerate more discrepancies in smile esthetics than younger groups, except for gingival exposure >6 mm during the smile (considered nonesthetic by all age groups). By contrast, the influence of gender on the esthetic perception of smiles is considered insignificant in the literature [30,48,49,54,55]. In this study, most studies only briefly described the participant's gender, while the others omitted the subject. At most, by reading the results, we can say that there is a tendency for females to prefer narrower teeth and a greater step between the edge of the remodeled canine and the edge of the reference central incisor [48], and females tend to give higher scores [49], but differences may be highly culture-dependent [4].

4.3. Digital and Real Models

Both digital and real models have advantages and disadvantages. The main benefit of the digital model is the absence of confounding variables. Produced by computerized handling and performed from an initial 2D virtual image or a clinical photograph, it maintains the same teeth and lips, and therefore the same smile, introducing only slight variations. However, digital representations do not fully represent actual clinical situations in daily life, making it difficult to perceive the image and its appreciation [16]. The data obtained in this review show a tendency for higher ratings when this method is employed, because the images appear more perfect, which is a source of involuntary bias. A real model has the advantage of representing reality in images, similar to daily clinical situations, and it does not follow a standard or reference. In contrast, eliminating distraction variables due to individuality is impossible with different teeth, lips, and smiles. These natural features distract the viewer, biasing the evaluation with a tendency to identify more anatomical defects, which may justify the lower ratings.

To minimize these differences, some studies have focused on the lower face, overlapping the same lips in different agenesis phenotypes [6,16,18]. In contrast, others digitally morphed a female model to represent the most prevalent type of that gender [9,14]. Studies that used real models [7,19,49,50] failed to eliminate confounding variables with an inherent evaluation bias. The digital manipulation of a real model with the elimination of confounding variables using the same lips, teeth, and face was formerly proposed [9] to allow a perception closer to reality through the real model. A similar methodology with minor digital manipulations over an original photograph to obtain a range of simulations has been identified [25,48,51,52].

A transversal constraint found in most studies is the restricted time for image observation (a few seconds), which allows only the observer's first impression, probably biassing a score that could change with a more extended viewing period.

4.4. Rating Scales

The use of rating scales that were not directly comparable forced a fundamental convenience scale conversion but was a limitation. The VAS allows for a wider value choice, with the selection of values on a non-numeric reference scale with possible fractional values, which is unlikely with the 0–10 scale with only unique integers. This was the most relevant limitation of this systematic review, because it forced the adaptation of the results with no bibliographic references to support this conversion. In addition, two studies [49,50] used a scale of 0 to 5, which further strengthened the results. Another pertinent conversion was from the quantitative scale of the mean with standard deviation [7,14,16] or the median [9] to the mean with a 95% confidence interval, given in only one study [18]. However, this conversion is supported [44,45], allowing for the comparison of values in the same units of measurement, making the values comparable. Future studies could adopt a numeric rating scale (NRS) to standardize the evaluation of subjective perception of smile esthetics. VAS and NRS are concordant for evaluating both extra- and intra-oral images, are not influenced by differences between evaluators, and are simple methods; however, NRS is easier to deal with [56].

4.5. Smile Evaluation

The lack of significant differences ($p < 0.05$) between the two types of treatment found in the "Opening vs. Closure" group (Figure 2a,b and Supplementary Table S2) may be explained within each study by the inability of laypersons to detect subtle differences between situations, ranking both types of therapy with high scores [7,18]. However, in the inter-article classification, there was a discrepancy between the absolute results, which can be explained by the different scales and subsequent scale conversions. Nevertheless, the results indicated that both treatments achieved similar esthetic results ($p < 0.05$) [7,18]. In the group "No remodeling vs. Dental remodeling vs. Dental and gingival remodeling"-Unilateral (Figure 3a,b), the main differences existed between the presence or absence of symmetry, especially perceived by laypersons, to whom the most important factor is the symmetric morphology of the canine compared to the contralateral incisor when space closure is performed. Furthermore, mimicry between the lateral incisor and canine was valued more by laypersons than by dental professionals ($p < 0.05$). In contrast, the value of gingival remodeling was similar to that of isolated dental remodeling ($p < 0.05$). Paradoxically, for bilateral [9,16] and unilateral treatment [9], these authors found a reversal in the results obtained by laypersons and by the different groups of professionals, with laypersons scoring better images of "no remodeling" and "dental remodeling", as seen more recently [51], a result not observed for images of "dental and gingival remodeling."

The greater ability to detect details and greater technical demands of professionals due to specific training could explain this reversal, or perhaps laypersons' lack of perception of the changes in gingival margins may account for the reversal instead. Thus, gingival remodeling of canines should be weighed because it often requires supplementary orthodontic techniques, such as canine extrusion or premolar intrusion, gingival zenith change, and sometimes extensive coronary recontour [14], or even the need for mucogingival plastic surgery. Laypersons undervalue these procedures, and tolerate asymmetries of the gingival margin at the level of the central incisors up to 2 mm [9], the threshold for professionals being only 0.5 mm [9]. Given this fact and knowing that the asymmetries are more notorious closer to the midline, we can consider tolerable small asymmetries between the lateral incisors and canines [8]. To minimize differences in assessments, some authors [9,14] have used laypersons with advanced academic studies to approach the professional population. These differences remained, suggesting that professional training could be the primary key to valuing a smile. Regardless of the chosen treatment, if the agenesis is bilateral and attains a symmetrical treatment result, the result is accepted as esthetic, with higher global scores consistent with results from previous studies [8,18,34]. Therefore, one should seek symmetry in relation to the midline, knowing that, on average, orthodontists are more able to detect midline deviations exceeding 2 mm, while laypersons only notice variations greater than 3 mm [16,34].

4.6. Canine Morphology

Despite some limitations (canine esthetic variables changed separately and not as a whole and qualitative rating), one study [6] allowed us to understand how the width, height, morphology, color of the canine crown, and height of the gingival margin can alter the classification by itself. It was concluded that laypersons prefer narrower canines and value brighter hues than professionals. The existence of a positive correlation between the darkest canines and less attractive smiles, a fact recently highlighted [51,52], indicates that a simple change in the canine color hue makes smiles more attractive. A similar result was recently described in a study that focused on the perceptions of dental dyschromia according to patients and dentists, although it was not related to agenesis [57].

However, there is no consensus regarding the width of the canine as a substitute. Gomes and Pinho [25] partially contradicted two others [6,52], observing that all groups of observers preferred broader canines in a digitally manipulated specific clinical situation (asymmetric mesialized canines with differences in shape, color, and gingival contour). Notably, that study [25], despite having used a rule to distinguish canines as smaller or larger, had a ruler description that was somewhat confusing, without tangible value as a reference, preventing a more informed comparison between studies. Another study [52] also raised doubts about the width parameters as it used the original canine as an initial reference, raising doubts about matching these actual dimensions with those occurring in an average population. To overcome this, future studies should routinely use the canine width compared with the central incisor in the frontal view, as previously suggested [30,58]. Therefore, there is an urgent need for more extensive studies and randomized clinical trials. The divergence in these results may also be related to temporal changes in esthetic concepts or even to the geographic origins of perceivers, as has been suggested [59] since the participating populations were from different cultural roots, or the divergence may perhaps be related to the chosen substitute canine edge width or height [48], possibly affecting esthetics in the treatment of maxillary canine substitution. Additionally, the subjectivity of esthetic perception and possible changes based on the shared beliefs and standards of a specific community cannot be forgotten.

Li et al. [48] found that a canine with an edge width of 62.5% of the central incisor width and an edge height of 0.5 mm gingival to the central incisor edge was considered the most esthetic shape for the canine. Orthodontists do not appreciate marked cusp slopes (>1.0 mm) [48]. Simultaneously, laypersons preferred cusps between 1.0 and 1.5 mm. These results for laypersons have been reported [13] along with the lack of esthetic impact of the wear of the canine cusps, a detail that could favor a slight step between the edge of the substitute canine and the edge of the central incisor [48,60]. Recently, it was found [55] that when the lateral incisor was the mater, laypersons preferred wider teeth, with tendencies for measurements far beyond the 62.5% reference of the golden width/height proportion, the relationship most valued by orthodontists.

This systematic review has revealed that standardized and randomized clinical trials are still needed to compare symmetrical MLIA space opening or closure and to evaluate asymmetrical situations with the need to use the same rating scale. Given the data obtained, dental professionals must abstain from giving their personal opinions when recommending treatment options for an MLIA situation because discrepancies exist between the treatment result judged as most esthetic and that most likely to be recommended.

4.7. Different Options for MLIA Management

Based on all the data collected, the management of maxillary lateral incisor agenesis in a growing young population can include (1) monitoring because in some cases, no treatment may be necessary if the missing tooth does not affect the patient's dental health, function, or esthetics (in these cases, the mesial drift of the canine is allowed); (2) space maintenance to prevent the adjacent teeth from drifting into the empty space, preferably with a fixed tooth-shaped space maintainer until a permanent replacement tooth can be placed; and (3) orthodontic treatment depending on the severity of the misalignment, the planned closure or space opening, or other orthodontic issues. In young adults and adults, besides those options, there are two alternatives: (4) a single-tooth implant, preferably as late as possible to delay infraocclusion, or (5) tooth-supported restoration in the form of a dental bridge with one or two supporting wings.

5. Conclusions

The esthetic perception of MLIA treatment is controversial, even among professionals. Laypersons cannot value space opening versus space closure and value symmetry. Orthodontists are among the most demanding professionals in line with their expertise in the area. Gingival remodeling was not significantly more valued ($p < 0.05$) than isolated dental remodeling. In doubtful situations, a discussion with a less demanding patient is pertinent. Therefore, dentists should avoid overtreatment. Randomized clinical trials are still needed to compare symmetrical MLIA space opening or closure and to evaluate asymmetrical situations. Comparable rigorous methodologies, such as the standardization of the group of observers and rating scale, are needed.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/dj11040105/s1: Table S1: Difference in means and size effect calculation; Table S2: Paired *t*-test run on the type of treatment subgroup (space opening versus space closure); Table S3: Paired *t*-test run by type of remodeling (canine without remodeling, canine with dental remodeling, and canine with dental and gingival remodeling); Table S4: Shapiro-Wilk test of normality: (a) by type of treatment; (b) by type of re-modeling; Figure S1: Forest plots with differences in means, by author and: (a) type of remodeling, (b) type of agenesis, (c) observer; Figure S2: Boxplots for the identification of significant outliers: (a) Opening versus closure data; (b) Unilateral agenesis; (c) Bilateral agenesis.

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SYSTEMATIC REVIEW

Impact of in vitro findings on clinical protocols for the adhesion of CAD-CAM blocks: A systematic integrative review and meta-analysis

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ABSTRACT

Statement of problem. Computer-aided design and computer-aided manufacturing (CAD-CAM) blocks have evolved rapidly, making it difficult to establish the best clinical protocol for bonding a given block and whether an established protocol is appropriate for a newly introduced product.

Purpose. This integrative systematic review and meta-analysis aimed to clarify whether the clinician can select the most efficient adhesion protocols for CAD-CAM blocks by reading published in vitro studies and implementing them in daily practice.

Material and methods. Based on the population, intervention, comparison, and outcome (PICO) strategy, 3 databases were searched for in vitro studies, randomized clinical trials, prospective or retrospective studies, and case reports from January 1, 2015, to July 31, 2021. A meta-analysis analyzed 28 studies to calculate the mean difference between best and worst protocols for each author and block with a random-effects model (α=.05).

Results. From 508 relevant studies, 37 in vitro studies, 2 clinical studies, and 1 clinical report were selected for data extraction and qualitative analysis. Vita Enamic, IPS e.max CAD, LAVA Ultimate, and Vita Mark II blocks were the most studied, and RelyX Ultimate was the most used luting cement. The meta-analysis confirmed the null hypothesis that the evidence-based efficacy of clinical protocols to bond CAD-CAM blocks is still controversial (P<.05).

Conclusions. There are objective standards for individual in vitro tests, but the studies lack standardization. Some tested protocols were more efficient than others. Randomized clinical trials and well-documented clinical situations were almost nonexistent, making direct application of in vitro findings in clinical practice impossible. (J Prosthet Dent 2022;■:■-■)

Computer-aided design and computer-aided manufacturing (CAD-CAM) is becoming common in restorative dentistry, facilitating the manufacturing and delivery of indirect esthetic restorations.[1-5] CAD-CAM allows 3D modeling, chairside milling of restorations,[6] and predictable single visit[3] restorations with excellent fit and mechanical properties,[4,7] contrasting with operator-dependent laboratory-made restorations with a high variation of mechanical and esthetic properties.[8-10] The quality, bond strength, and clinical longevity of CAD-CAM restorations appear to have increased, with contemporary restorations having excellent performance.[11]

CAD-CAM blocks for indirect esthetic restorations are typically made from ceramic or composite resin.[3,6] Composite resins have more straightforward fabrication and favorable properties, with lower hardness, lower elastic modulus, and straightforward cementation.[7] High-strength monolithic zirconia materials are also available for CAD-CAM technology, with no need for esthetic porcelain veneering.[9,12] This allows restorations with a thickness of 0.5 mm or less and minimal antagonist wear, less than with other ceramic or metal-ceramic restorations.[12] Bonding is essential for CAD-CAM

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Clinical Implications

Clinicians must conscientiously update adhesive protocols and techniques for each new material based on the manufacturer's instructions. Technical requirements may differ for similar products within the same brand and even for products with similar names from other brands.

indirect restorations, both ceramic and composite resin, as they rely on adhesion for retention and strength, both of which directly affect their longevity.[2,6] Catastrophic, partial, or chipping fractures are the most common failures reported.[3,13] High retention, microleakage prevention, and enhancement of marginal adaptation are characteristics of a resilient and durable adhesive bond.[6]

Recent advances in chemical modification of the composite resin cement with, for example, the introduction of antibacterial agents and multifunctional monomers improved the adhesive bond strength to dentin, enhancing long-term performance and protecting the tooth-adhesive interface from microleakage.[1] The optimal surface treatment for interface substrates and the best luting cement, restoration material, and dentin bonding agent to produce the highest bond strength is unclear. A consensus regarding the optimal adhesive protocol is lacking.[11,14] Composite resin cement has been used for its advantageous mechanical and adhesive properties to cement conventional metal crowns, fixed partial dentures, ceramic crowns, veneers, or to repair fractured metal-ceramic, ceramic, and composite resin restorative materials.

The composition of CAD-CAM blocks influences the bond strength of the ceramic material, and the mechanical and chemical interactions between the substrate and the bonding agent.[11] Surface treatment and its selection depend on the chemical and physical properties of each material.[15] A combination of mechanical and chemical strategies has been the most accepted procedure for enhancing the composite resin cement-to-glass–ceramic bonding.[16] Silane provides chemical adhesion to silica-containing ceramic substrates. In addition, acid etchants, such as hydrofluoric acid, can partially dissolve the glassy phase, improving mechanical interlock with the composite resin cement.[15] A consensus regarding the optimal bonding of monolithic zirconia materials is lacking.[15,17]

As various factors can influence the bond's quality and the adhesion mechanism's physical characteristics,[15,17,18] several in vitro studies have evaluated the effect of different pretreatments on adhesion between restorative materials and dentin.[2,11] Nevertheless, some have technical limitations for clinical use. Furthermore, many tested techniques are difficult to compare from the studies.[2] For clinicians, selecting the ideal surface treatment protocol or adequate luting agent for each material is a significant concern as they are aware of its influence on the long-term success of the restoration.

This integrative systematic review and meta-analysis aimed to determine whether a clinician can select the most efficient adhesion protocol for each CAD-CAM block by reading published in vitro studies and implementing them in daily practice. In addition, the in vitro adhesion of CAD-CAM blocks reported in the literature was compared with the in vivo efficacy of the protocols. The research hypotheses were that the clinical protocols for CAD-CAD block adhesion would be well established and clinically reproducible or that the evidence-based efficacy of clinical protocols to adhere CAD-CAM blocks would remain controversial.

MATERIAL AND METHODS

The review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 recommendations.[19] The population, intervention, comparison, and outcome (PICO) question was as follows: "Do in vitro findings influence the clinical protocols for the adhesion of CAD-CAM blocks?" The CAD-CAM blocks constituted the population. The intervention was defined as the adhesion protocol performed on the block or teeth for cementation; specifically, teeth or block surface treatment, type of block, coupling agent, and luting cement. The comparison was made between protocols for each CAD-CAM block to find intrastudy and interstudy differences in the mechanical performance. Clinical protocols were the outcome.

A bibliographic search was carried out in the databases Medline/PubMed, ScienceDirect, and EBSCOhost, with keywords combined in the Boolean expression: [(CAD-CAM) AND (adhesive OR adhesion OR bonding OR cement) AND (ceramics OR blocks) AND protocol], filtered by the English language. Inclusion criteria were research papers, randomized clinical trials (RCTs), and clinical cases that addressed the theme, published from January 1, 2015 to July 31, 2021, with accessible full text. Duplicates and papers published before 2015 were excluded.

Retrieved pertinent systematic reviews and reviews were not included in the qualitative analysis, but were still included in the study. Also included were those found by manual search, done by pairing each key word with the word CAD or by searching the reference lists of the included articles to allow comparisons, and broadening of the introduction and discussion sections. Duplicate articles were preliminarily withdrawn with a citation manager (EndNote X8 Windows; Clarivate). Articles were then filtered by title, abstract, and complete

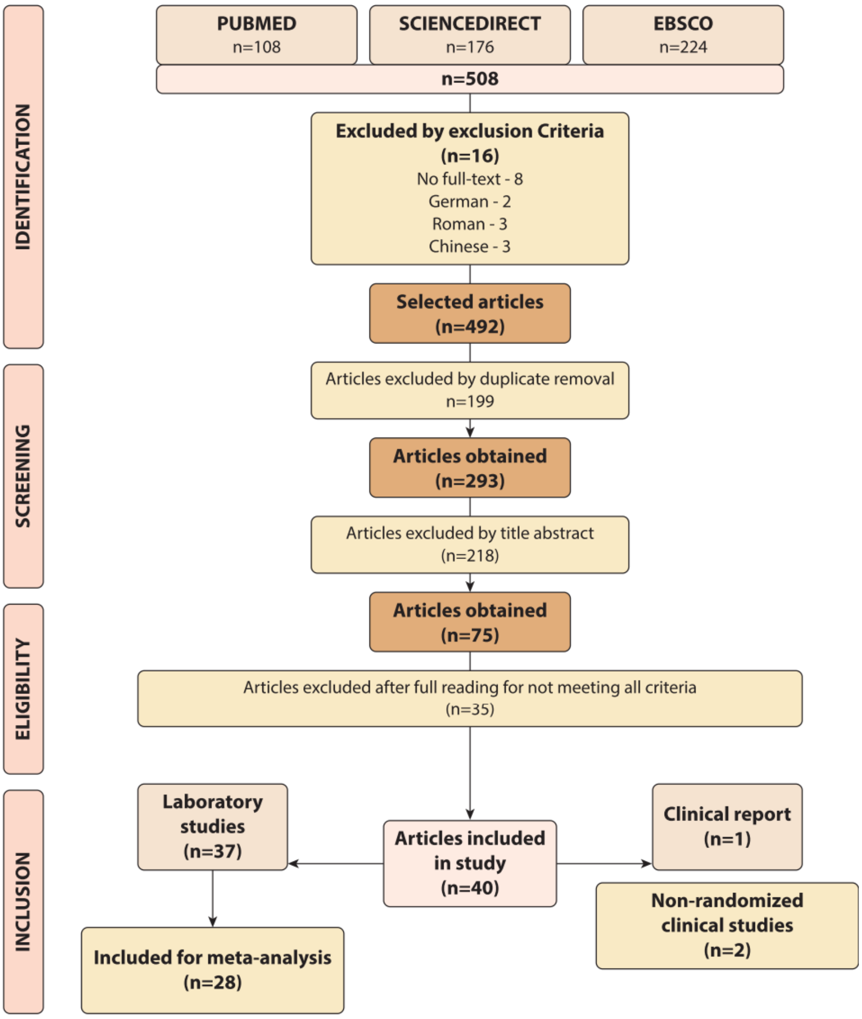

Figure 1. Flow diagram of study selection according to preferred reporting items for systematic reviews and meta-analysis statement.

reading, agreeing with the PRISMA Statement, as shown in Figure 1. Two investigators (M.J.C.L., R.C.) independently selected each pertinent article for detailed reading. A third investigator (T.P.) resolved disagreements.

Qualitative analysis for risk of bias assessment was done by individually scoring the 10 elected parameters within the following criteria: (0) clearly mentioned, (1) present but not accurately mentioned, and (2) not mentioned. Global scoring was categorized as Low Risk (0-4), Medium Risk (5-12), High Risk (13-17), and Very High Risk (18-20) of bias. The SJR score (Q1-Q4) was assigned by publication date for each study. The quality assessment of the observational studies was done by an adapted grading of recommendations, assessment, development, and evaluations (GRADE) method.[20] Data extraction was summarized in tables. Pertinent information was examined in comprehensive graphics after applying the following filters: type of CAD-CAM block tested, luting material used in the laboratory and in vivo tests, mechanical test used for bonding strength evaluation, light source intensity, type of surface treatment, and coupling agent.

A meta-analysis focused on adhesive strategies for each type of CAD-CAM block was conducted using a software program (Stata v17.0; StataCorp). Subgroup analyses were performed to assess the different kinds of surface treatment methods, adhesive joint substrates, and types of mechanical tests, and, for all studies that

Table 1. Synthesis of qualitative analysis for risk of bias assessment

Study	Abdou et al, 2021[21]	Cardenas et al, 2017[13]	Ceci et al, 2015[11]	Demirel et al, 2019[23]	De Oliveira et al, 2018[22]	Dos Santos et al, 2019[24]	El-Damanhoury et al, 2017[25]	Elsaka et al, 2020[18]	Elsayed et al, 2017[26]	Emsermann et al, 2019[27]	Frankenberger et al, 2015[28]	Ilie et al, 2019[29]
Specimen Randomization	0	0	0	0	0	1	0	0	0	0	0	1
Single Operator	2	0	0	2	2	2	2	2	2	2	2	2
Operator Blinded	2	2	2	2	2	2	2	2	2	2	2	2
Standardized Specimens	0	0	0	0	0	0	1	0	0	0	0	0
Control Group	0	2	2	0	0	2	0	0	0	0	0	2
Fractographic analysis	0	0	0	0	0	1	0	0	0	0	2	0
Manufacturer's Instructions	0	0	0	0	0	0	0	1	0	0	0	0
Sample Size Calculation	2	2	2	2	2	2	2	2	2	2	2	2
International Standards	1	1	1	1	0	1	1	0	1	1	0	0
Proper statistical analysis	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	7	7	7	7	6	11	8	7	7	7	8	9
Risk of Bias	M	M	M	M	M	M	M	M	M	M	M	M
Journal SJR score by the date of publication	(Q2)	Q2	Q2	NS	Q1	Q1	Q1	Q1	Q2	Q1	Q2	Q1

Study	Ishii et al, 2017[30]	Kalavacharla et al, 2015[31]	Kassem et al, 2020[32]	Komoto et al, 2021[33]	Liebermann et al, 2019[34]	Lümkemann, 2020[35]	Monteiro et al, 2020[36]	Murata et al, 2018[37]	Murillo Gúmez et al, 2017[16]	Nejat et al, 2018[38]	Φilo et al, 2015[17]	Passia et al, 2015[39]	Peumans et al, 2016[6]
Specimen Randomization	1	1	0	1	1	1	1	1	0	0	0	1	0
Single Operator	2	2	2	2	2	2	2	2	2	2	2	2	2
Operator Blinded	2	2	2	2	2	2	2	2	2	2	2	2	2
Standardized Specimens	0	0	0	0	0	0	0	0	0	0	1	0	0
Control Group	0	0	0	0	2	1	0	0	0	0	0	2	0
Fractographic analysis	0	2	2	0	0	0	0	0	0	0	0	0	0
Manufacturer's Instructions	0	0	0	0	0	0	0	0	0	1	0	0	0
Sample Size Calculation	2	2	0	2	2	2	0	2	2	2	2	2	2
International Standards	1	1	1	1	1	0	1	0	1	1	1	1	1
Proper statistical analysis	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	8	10	7	8	10	8	6	7	7	8	8	10	7
Risk of Bias	M	M	M	M	M	M	M	M	M	M	M	M	M
Journal SJR score by the date of publication	Q2	Q1	NS	(Q1)	Q1	Q1	Q1	Q2	Q1	Q2	Q1	Q1	Q1

Study	Rigos et al, 2018[40]	Roperto et al, 2016[41]	Sakrana, 2017[42]	Shinohara et al, 2017[43]	Şişmanoğlu et al, 2020[3]	Siqueira et al, 2019[45]	Silthampitag et al, 2016[44]	Tekçe et al, 2017[46]	Trindade et al, 2016[47]	Ustun, 2020[48]	Wu et al, 2018[49]	Yazigi et al, 2017[50]
Specimen Randomization	0	1	0	1	0	0	0	2	0	1	0	0
Single Operator	0	2	2	2	2	0	2	2	2	2	2	0
Operator Blinded	2	2	2	2	2	2	2	2	2	2	2	2
Standardized Specimens	0	0	0	0	1	0	0	1	0	0	0	1
Control Group	2	2	0	0	0	0	0	0	0	0	0	1
Fractographic analysis	0	2	0	1	2	0	0	0	0	1	0	1
Manufacturer's Instructions	0	0	0	2	0	0	2	0	0	0	0	0
Sample Size Calculation	2	2	2	2	2	0	2	2	2	2	2	2
International Standards	0	1	1	1	0	1	1	1	1	1	1	1
Proper statistical analysis	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	6	12	7	11	9	3	9	10	7	9	7	8
Risk of Bias	M	M	M	M	M	L	M	M	M	M	M	M
Journal SJR score by the date of publication	Q1	Q3	Q3	Q2	Q2	Q2	Q1	Q1	Q1	Q1	Q1	Q1

NS, Not scored; Q1, First quartile; Q2, Second quartile; Q3, Thrid quartile; ( ) - Quartile in the previous year. Green- good score/low risk, orange- average score/medium risk, red- bad score/high risk.

evaluated more than 1 type of CAD-CAM block or more than 1 surface treatment method, each type of material or treatment method was considered independently.

The statistical heterogeneity was detected using the I^2 statistic test (α=.05). A subgroup was formed with the 28 articles that studied the 9 most tested blocks in at least 2 in vitro studies. A meta-analysis was conducted by the authors and CAD-CAM block to find intrastudy heterogeneity and protocol splitting by efficiency after calculating the difference between means and the effect size (α=.05; 95% CI; Z-value=1.96). Funnel and Galbraith plots assessed the publication bias and heterogeneity (random-effects model; α=.01; 99.9% CI; Z-value=2.58).

RESULTS

The search retrieved 508 articles (Medline/PubMed [108], ScienceDirect [176], EBSCOhost [224]). After applying inclusion and exclusion criteria, 37 in vitro studies,[3,6,11,13,16-18,21-50] 2 non-RCTs,[51,52] and 1 clinical report[53] were selected. The manual search retrieved 3 systematic reviews with meta-analysis,[1,9,12] 4 systematic reviews,[2,7,14,15] 3 reviews,[4,5,10] and 1 survey.[54] The qualitative analysis for risk of bias assessment (Table 1) revealed 1 low-risk[45] (2.7%) and 36 medium-risk of bias (97.3%) articles. Transversal factors for lower score were the absence of operator blindness (referred to in 1 article[13] [2.7%]), no sample size calculation (referred to in 3 studies[29,32,45] [8.1%]), and no reference to a single operator (referred to in 5 studies[11,13,40,45,50] [13.5%]). Specimen randomization and the control group were frequently inadequately described or lacking. The level of evidence of the 2 observational studies is shown in Table 2. Given the parameters, the non-RCTs were scored as very good[52] and good[51] (mainly because of the dropout percentage, a known cause of bias). The clinical report[53] achieved good quality (within the scientific knowledge and manufacturer's instructions despite not using a dental dam, and given the periodontal health, supragingival margins, and a cooperative patient).

Data extraction from in vitro and in vivo studies is shown in Tables 3 to 6. The authors identified 686 protocols to adhere 37 different CAD-CAM blocks (Supplementary Table 1 available online). Filtered data are displayed in Figures 2 to 7. The meta-analysis with the initial 37 selected in vitro studies, combining various

Table 2. Methodological evaluation of studies according to grading of recommendations, assessment, development, and evaluations method (adapted scale of 0-20)

Items	Criteria	Application
Risk of bias	Randomized or observational	[-1] J-risk of serious bias [-2] • very serious
Inconsistency of results (heterogeneity)	Assessment of similarities and estimates	[-1] important inconsistency
Indirect evidence	Evaluation of the presence of differences in the population, intervention and outcomes between the Included studies and the review question	[-1] - serious indirect evidence [-2] - very serious
Imprecision	Sample dimension	[•1] ifn<50, [-2] ifn<30
Publication/methodology bias	Lack of methodological information	[-1] suspicion of publication bias or lack of information
Weighting for observational studies		
Impact of the Journal	Evaluation of the impact of the journal	Maximum impact (Q1) - [+2]
Variation in relation to the average of studies in the held work	Evaluation of variation of the Identical studies	On average of identical studies •1+2]
Effectiveness of the treatment	Evaluation of effectiveness	Good clinical performance [+2]
Sample size	Evaluation of the sampled size of the study	If >50 - [+2J]: if >30 - [+1]
Well-founded study	Assessment of the rationale of the article	Well-founded [+2]

	Archibald et al, 2017	Spitznagel et al, 2018
Bias risk (randomized or observational)	3	3
Inconsistency of results (heterogeneity)	-	-
Indirect evidence	-	-
Imprecision	-	-
Methodology	2	2
Weighting for observational studies		
Journal Impact (+2ifQ1)	2	2
Effect with % within the range of other studies in the field (42)	2	2
Effectiveness of the CAD-CAM block (+2)	2	2
Sample size (+2 >50) (+1 >30)	2	2
Rationale for the study (+2)	2	2
Percentage of dropouts (+2 <20%) (-2 >40%)	-2	2
TOTAL	13	17

agents of the adhesive strategy, revealed very high heterogeneity (I^2>99%) in all attempts, even with a random-effects model (α=.05), and gave illegible graphics because of the large number of entries; therefore, results are not displayed. The meta-analysis based on the difference between means and effect size (*P*=.05; 95% CI; Z-value=1.9599) (Supplementary Table 2 available online) conducted by data filtering is shown in the forest plots (Fig. 8 and 9). Overall, tested protocols performed better than control protocols, but differences were evident. The IPS e.max ZirCAD bonding to substrates was not consistent in various studies with the need for simultaneous physico-chemical treatment of the block surface, and immediate dentin sealing (IDS) with a universal self-adhesive followed by a low-viscosity resin-matrix restorative favored adhesion to the tooth. As a second joint substrate, only composite resin bonded to IPS e.max ZirCAD raised concerns.

The meta-analysis combining the selected 28 articles,[3,6,11,13,16,18,21,23,25,27-35,37,39,41,42,45-50] based on the difference between means and the effect size (*P*=.05; 95% CI; Z-value=1.9599) is represented in Figure 10. For the most tested blocks, best and worst adhesion protocols were identified (Table 7). Supplementary Tables 3 and 4 (available online) show more and less favorable protocols. Figure 11 shows the highest and lowest mean results obtained according to the test and joint substrate. Assessment of publication bias and heterogeneity is shown in Figures 12 and 13. The funnel plot asymmetry suggests an overestimation of the intervention effect, probably induced by the disparity between samples, with some possible bias. Studies that tested composite resin or luting cement as the second joint substrate and those that used microshear bond strength (µSBS) or microtensile bond strength (µTBS) tests had more publication bias. The Galbraith plot suggests an absence of substantial heterogeneity among the effect size (only 2 studies outside the 99.9% CI region). All studies had high precision (toward the right on the X-axis). Globally the studies were above the green line with the red line sloping upward, suggesting favorable tested protocols compared with the control protocol.

DISCUSSION

This review accessed whether in vitro findings concerning the strength of the bonding between CAD-CAM blocks and different substrates could be easily perceived

Table 3. Resumed data extraction from the selected in vitro studies

Author, y	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Sample Pairing	Type of Test and Procedures
Abdou et al, 2021[21]	Estelite Block EsteliteP Block Katana Avancia Katana AvanciaP KZR-CAD HR2 KZR-CAD HR3 Lava Ultimate Tetric CAD Vita Enamic	9.6% HF -60s Al2O3 50 µm/??s/10 mm /0.2 MPa	Clearfil Ceramic Primer Plus	Clearfil Tri-S Bond ND Quick Clearfil Tri-S Bond ND Quick + Porcelain Bond Activator	PanaviaV5	Block to Block (n=6)	µTBS MPa Light polymerization 1400 mW/cm^2 24 h Water
Cardenas et al, 2017[13]	IPSe. max CAD	5% HF -20s	No silane Monobond Plus MonobondS Prime & Bond Elect	No adhesive system Scotchbond UA	RelyX Ultimate Enforce	Block to Luting cement (n=10)	µSBS MPa Light polymerization 1200 mW/cm^2 24 h or 1 y (37 °C) - Water
Ceci et al, 2015[11]	Lava Ultimate	SiC paper −600 grit No acid 35%H3PO4 −15s Glycine powder -30 s No glicyne powder	Scotchbond UA No treatment	Scotchbond UA	RelyX Ultimate RelyX Unicem2	Block to Bovine dentin (n=10)	µSBS MPa Light polymerization 1000 mW/cm^2 24 h -Saline solution
Demirel et al, 2019[23]	Cera Smart Lava Ultimate Shofu Block Vita Enamic	SiO2-coated Al2O3 30 µm/10s/10 mm/ 0.28 MPa	N/A	Porcelain Primer+Adapter Single Bond Universal Single Bond-2 All Bond Universal Clearfil Universal Bond	N/A	Block to Resin composite (n=11)	µSBS MPa Light polymerization >1000 mW/cm^2 5 °C-55 °C −5000c
De Oliveira et al, 2018[22]	Trinia	Al2O3 45 µm/10s/10 mm/ 0.2 MPa 37%H3PO4 -30s	Cera-Resin Bond	All Bond3	C&B Resin Cement	Block to Human dentin (n=15)	SBS MPa + µTBS MPa 24 h - Water Light polymerization >380 mW/cm^{2}37 °C -500 000c 5 °C-55 °C -500c
Dos Santos et al, 2019[24]	IPSe.max ZirCAD LT	Al2O3 50 µm/15s/?? mm/ ?? MPa SiC -180/220/440 /600 grit	Z Prime Plus	Scotchbond UA All Bond Universal Z-Prime Plus + All Bond Universal	Z350 XT composite resin	Block to Resin composite (n=10)	µSBS MPa24 h - Water Light polymerization 1200 mW/cm^2
El-Damanhoury et al, 2017[25]	IPSe.max CAD Vita Enamic Vita Mark II	No treatment 4.8% HF 20s (e.max) or 60s (Enamic/Mark II) Monobond Plus	No treatment Monobond Plus	Monobond Plus Monobond Etch & prime	MultilinkN automix dual-cure resin cement	Block to Luting cement (n=10)	SBS MPa24-h Water Light polymerization 1200 mW/cm^2 -20s 5 °C-55 °C -5000c
Elsaka et al, 2020[18]	GRANDIO Block Lava Ultimate Vita Enamic	No treatment Al2O3 45 µm/5s/10 mm/ 0.2 Mpa Silane -60s 9% HF -60s Titanium tetrafluoride	Silane (Ceramic Bond)	N/A	Bifix QM	Block to Block (n=20)	µTBS MPa24h (37 °C) - Water 5 °C-55 °C -0 and5000c
Elsayed et al, 2017[26]	IPSe. max CAD Zenostar	SiC -600 grit Al2O3 50 µm/??s/10 mm/ 0.1M Pa 5% HF -20s	Monobond Plus Calibra Silane	Scotchbond UA All Bond Universal OptiBond XTR Kerr Prime and Bond NT	Variolink Esthetic DC RelyX Ultimate NX3 Duo-Link Universal Calibra Esthetic	Block to Luting cement (n=24)	µTBS MPa Light polymerized 650 mW/cm^2 -2 ×20s +90s3d (37 °C)/Water +0c30d (37 °C)/ Water +7500c 150d (37 °C)/Water +37 500c
Emsermann et al, 2019[27]	Brilliant Crios Cerasmart Gradia Block Lava Ultimate Vita Enamic	SiC -180-grit SiO2-coated Al2O3 -30 µm/5s/10 mm/ 0.2M Pa Al2O350 µm/5s/10 mm/ 0.15 MPa 5% HF -60s	Ultradent Silane G-Multi Primer GC-Primer Vitasil Silane	Scotchbond UA One Coat7 Universal	RelyX Unicem2 Duo Cem G-Cem LinkForce RelyX Ultimate	Block to Luting cement (n=24)	µSBS MPa Light polymerized 1200 mW/cm^2 -3 ×20s6m (37 °C) -Demineralized water

(*continued on next page*)

Table 3. (*Continued*) Resumed data extraction from the selected in vitro studies

Author, y	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Sample Pairing	Type of Test and Procedures
Frankenberger et al, 2015[28]	Celtra Duo IPSe. max CAD Lava Ultimate Vita Enamic	No treatment Al2O3 50 µm/10s/5 mm/?? MPa 5% HF -20/30 or60s	Monobond Plus	Prime & Bond XP + SCA (self-cure activator)	Calibra RelyX Unicem2	Block to Luting cement (n=24)	µTBS MPa Light polymerized 1200 mW/cm^2 -60s +80s24h (37 °C) -Water 5 °C-55 °C -10 000c
Ilie et al, 2019[29]	Tetric CAD HT	SiC papers 60,320, and600 grit	N/A	Adhese Universal	Variolink Esthetic LC	Block to Luting cement (n=24)	µSBS MPa Light polymerized 1313.60 (±11.41) mW/cm^2 24 h (37 °C) -Water 5 °C-55 °C -10 000c
Ishii et al, 2017[30]	Lava Ultimate Vita Enamic Vita Mark II	32%H3PO4 -15s Al2O3 40 µm/10s/10 mm/ 0.15 MPa Scotchbond Universal Etchant	Scotchbond UA	Scotchbond UA Filtek Supreme Ultra - Flowable Restorative	RelyX Ultimate	Block to human molars (n=12)	µTBS MPa Light polymerized 700 mW/cm^2 -5 ×20s24 h (37 °C) -Water 37 °C -30 000c
Kalavacharla et al, 2015[31]	IPSe. max CAD	SiC papers −180/ 320 grit Al2O3 -0.5 µm/ 4x30s No treatment 5% HF -20s9.5% HF -60s	RelyX ceramic primer	Scotchbond UA	Z100 Composite resin	Block to Composite resin (n=10)	µSBS Light polymerized 1200 mW/cm^2 -4 ×20s24 h (37 °C) -Water

Al2O3, aluminum oxide; c, cycle; d, day; h, hour; HF, hydrofluoric acid; H3PO4, phosphoric acid; H2SO4, sulfuric acid; m, month. N/A, not applied; Scotchbond UA, scotchbond universal adhesive; SiC, silica paper abrasive; s, second; w, week; y, year; ??, not displayed.

by clinicians and incorporated into the daily clinical protocols, and was developed to integrate laboratory and clinical studies. Limiting the search to publications from the last 7 years restricted the review to materials used in contemporary clinical practice. Bias should not have occurred since, in the last 20 years, 70% of the articles were from that period. Based on the existing data ($P<.05$), the hypothesis that evidence-based efficacy for clinical protocols to adhere the different CAD-CAD blocks is still controversial, was accepted.

Given the descriptive results (Figs. 2–7), meta-analyses for each material subgroup were conducted. Still, as the technical protocol (specific sequence of technical steps) was the focus of this review, that methodology was abandoned, as the study would lose interest. Furthermore, as what should be chosen to be combined in a meta-analysis can be subjective and does not always fit into statistical solutions, after discussion, clinical judgment, and judicious consensus, a new meta-analysis focused on the best and worst adhesion protocols for each CAD-CAM block was carried out.

The tested protocols identified (N=686), reflected the search for solutions to deliver long-lasting functional and esthetic restorative treatments dependent on a stable union between the restorative material and the dentin,[13,21,26,30,32,33] in a practical and rapid way, as proposed in the 2 clinical trials.[51,52] However, the lack of systematization and standardization makes it difficult for clinicians to identify an evidence-based process that is easily reproducible in daily practice, as stated during the data extraction process (Tables 3-5). Despite that, there was agreement among authors on the importance of using appropriate luting cement, surface conditioners, and bonding agents to obtain durable restorations.[14,18,28,30] However, a survey[54] of German dentists showed the frequent use of inappropriate bonding methods, drawing attention to the benefit of establishing straightforward bonding protocols with clear evidence-based criteria.[26]

A medium score of risk of bias in most articles is the probable cause of some bias confirmed by the funnel plots (Fig. 12). Globally, the articles were well structured. The 2 articles[23,32] with no SJR score failed the 2021 criteria [Portal] (http://www.scimagojr.com)[55] but were still published in open access journals and included in the directory of open access journals (DOAJ) [Portal](https://doaj.org/),[56] a secure quality warranty for the clinician. Two studies[6,33] were excluded from the meta-analyses since the reported results did not allow a rigorous reading or statistical treatment.

Matching in vitro with in vivo studies had evident limitations. Of the 2 in vivo observational studies, 1 used pressed ceramic IPS e.max and IPS e.max CAD,[51] and the other[52] used the Vita Enamic block. Also, these studies were not randomized and had a significant number of patient dropouts (42%[51] and 21.3%[52] at 3.5 and 3 years, respectively). The materials in these studies matched the most tested blocks of the 37 in vitro studies. RelyX Ultimate, Variolink Esthetic, and Variolink II were the luting materials used, corroborating the trend of choice either for in vitro or in vivo studies.

Table 4. Resumed data extraction from the selected in vitro studies

Author, y	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Sample Pairing	Type of Test and Procedures
Kassem et al, 2020[32]	Ceramill COMP CeraSmart	5% HF -60 s Al_2O_3 25 µm/?? s/?? MPa 35% H_3PO_4 -None or 15 s	Silane coupling agent Ceramic Primer II	Scotchbond UA None on blocks (manufacturer's recommendation)	RelyX Ultimate	Block to Human dentin (n=8)	µ-TBS MPa Light polymerization Power not displayed − 20 s 5 °C-55 °C − 150 000 c
Komoto et al,[33] 2021	Vita Mark II	IDS Non-additional treatment Silane dry heating -20 s UV Light -20 s Visible Light -20 s	Rely X Ceramic Primer	IDS (Scotchbond UA + Filtek Supreme Ultra Restorative)	Rely X Unicem 2	Block to human molars (n=12)	µTBS MPa Light polymerized 1560 mW/cm^2 -2 ×20 s 24 h/30 d/90 d (37 °C) -Water
Liebermann et al, 2018[34]	Celtra Duo Initial LRF IPS e. max CAD Vita Mark II	SiC papers − 500/1200 9% HF 20, 30, or 60 s None (Monobond Etch&Prime)	Monobond Etch & Prime G-Multi Primer One coat 7 Scotchbond UA Prime & Bond Active	All-Bond Universal Clearfil Universal G-Multi Primer iBond Universal One Coat 7 Universal	Variolink Esthetic DC	Block to Luting cement (n=18)	TBS MPa Light polymerized 1200 mW/cm^2 -20 s 24 h (37 °C) - Distilled water
Lümkemann, 2020[35]	IPS e. max CAD IPS e.max ZirCAD LT Tetric CAD	Al_2O_3 50 µm/10 s/0.1 MPa < 5% HF - 20s 37% H_3PO_4 -15s	Monobond Plus Adhese Universal	Adhese Universal	Variolink Esthetic DC	Block to Luting cement (n=90)	TBS MPa Light polymerized 1200 mW/cm^2 − 20 s 24 h (37 °C) - Distilled water 5 °C-55 °C -20 000 c
Monteiro et al, 2020[36]	Lava Esthetic Fluorescent Full-Contour Zirconia	Al_2O_3 50 µm/10 s/10 mm/0.2 MPa SiO_2-coated Al2O3 -30 µm/10 s/10 mm /0.2 MPa	Scotchbond UA	Scotchbond UA	RelyX Ultimate	Block to human molars (n=11)	µTBS MPa Light polymerized 1102 mW/cm2 − 80 s 24 h (37 °C) -Distilled water 35 °C -240 000 c Thermal and pH cycling -10 000 c
Murata et al, 2018[37]	Vita Mark II	IDS 40% H_3PO_4 -5 s	PANAVIA V5 Tooth Primer Clearfil Ceramic Primer Plus Scotchbond UA	IDS (Scotchbond UA + Filtek Supreme Ultra Restorative)	Panavia V5	Block to human molars (n=16)	µTBS Light polymerized 700 mW/cm^2 − 5 ×20 s 30 min - (37 °C) - Water 37 °C -30 000 c
Murilo Gómez et al, 2017[16]	IPS e.max ZirCAD LT	Al_2O_3 50 µm/5 s/5 mm /0.2 MPa 10% HF− 20 s	None RelyX Ceramic Primer Clearfil Ceramic Primer Scotchbond UA	Scotchbond UA Adper Single Bond Plus	RelyX Ultimate	Block to Luting cement (n=18)	µSBS MPa Light polymerized 600 mW/cm^2 -40 s 24 h/6 m (37 °C) - Water
Nejat et al, 2018[38]	Experimental block	Al_2O_3 50 µm/10 s/10 mm /0.28 MPa 5% HF − 20 s	No primer Kerr Silane Primer Gluma (teeth)	OptiBond XTR Adhesive	Maxcem Elite	Block to human molars (n=10)	µSBS MPa Light polymerized 1100 mW/cm^2 − 10 s 1 h (37 °C) − Water 24 °C/water -100 000 c
Φilo et al, 2015[17]	Prettau Anterior (5Y-Z) Prettau Zirkon (3Y-Z)	Diamond disc -20 µm grain (Control) Al_2O_3 50 µm/10 s/10 mm /0.25 MPa KHF_2/10 min/ 280 °C	Monobond Plus All-bond Universal Scotchbond UA OptiBond XTR	Scotchbond UA Monobond Plus	RelyX Unicem	Block to SDR Flow+ (n=10)	µTBS MPa Auto (2 minutes) + light-cured - 5 ×20 s. Room temp. -15 minutes + 37 °C distilled water (24 ±2 h)
Passia et al, 2015[39]	IPS e.max CAD	SiC papers −600 grit 5% HF − 20 s	Monobond Plus All-bond Universal Scotchbond UA OptiBond XTR	Monobond Plus All-bond Universal Scotchbond UA OptiBond XTR	Multilink Automix Duo-Link RelyX Ultimate NX3	Block to MultiCore Flow DC (n=8)	µTBS MPa Light polymerized 650 mW/cm^2 − 40 s + (80 s lab curing unit) 3/30/150 d (37 °C) - Water 5 °C-55 °C -7500 c 37 500 times
Peumans et al, 2016[6]	Celtra Duo IPS e.max CAD IPS Empress CAD Lava Ultimate Vita Enamic Vita Mark II	SiC papers −320/600 grit Al_2O_3 27 µm/20 s/10 mm /0.28 MPa SiO_2-coated Al_2O_3 -30 µm/20 s/10 mm /0.28 MPa < 5% HF	Monobond Plus Heliobond	N/A	Clearfil Esthetic Cement Panavia SA Cement	Block to Block (n=5)	µTBS MPa Light polymerized 1100 mW/cm^2 − 4 ×40 s +4 ×60 s 24 h (37 °C) -Distilled water 1 w - micro specimens - Distilled water at 37 °C
Rigos et al, 2018[40]	BruxZir	IDS SiC papers -800/1000/1200 grit Al_2O_3 50 µm/10 s/10 mm/ 0.3 MPa SiO_2-coated Al_2O_3- 30 µm/10 s/10 mm/0.28 MPa 37% H_3PO_4 -15 s	Monobond S	IDS (Optibond FL)	Panavia F2.0 Perma Cem Dual Smartmix	Block to human molars (n=15)	SBS MPa Light polymerized 1250 mW/cm^2 24 h (37 °C) -Distilled water

Al_2O_3, aluminum oxide; c, cycle; d, day; h, hour; HF, hydrofluoric acid; H_3PO_4, phosphoric acid; H_2SO_4, sulfuric acid; IDS, immediate dentin sealing; KHF_2 - potassium hydrogen difluoride; m, month. NaCl, sodium chloride; N/A, not applied; Scotchbond UA, scotchbond universal adhesive; SiC, silica paper abrasive; s, second; w, week; y, year; ??, not displayed.

Table 5. Resumed data extraction from the selected in vitro studies

Author, y	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Sample Pairing	Type of Test and Procedures
Roperto et al, 2016[41]	Vita Mark II Paradigm	34% H_3PO_4 .30 s (enamel) + 15 s (dentin) No treatment 5% HF – 30 s Al_2O_3 50 µm/5 s/5 mm/?? MPa	Monobond Plus (2x 30 s)	Primer and Bond NT + Bond Activator Clearfil SE Bond None	Calibra Panavia F2.0 Smart Cem 2	Block to freshly extracted human molars - γ radiation 24 h (37 °C) - Water (n=30)	µTBS MPa Light polymerized Power not displayed 2 ×20 s 24 h (37 °C) -Distilled water
Sakrana and Özcan 2017[42]	Filtek Z250 IPS e.max ZirCAD LT	SiC paper -400 grit No treatment Al_2O_3 50 µm/?? s/10 mm/0.2 Mpa Methylene chloride Experimental solution	Monobond Plus	N/A	RelyX Ultimate Aplicap	Block to Filtek Z250 (n=20)	µTBS Light polymerization Power not displayed -20 s 24h (37 °C) -Distilled water Half of the sticks - no aging 5 °C-55 °C – 6000 c
Shinohara et al, 2017[43]	Gradia Block	SiC paper – 600 grit 40% H_3PO_4 – 5 s	Methyl methacrylate GC Ceramic Primer	Scotchbond UA	N/A	Block to Gradia Direct (n=8)	µSBS MPa Light polymerized Power not displayed – 40 s 24 h (37 °C) - Water Thermocycling 60 °C -zero/ 10 000 c
Siqueira et al, 2019[45]	IPS e. max CAD	5% HF None	Monobond Plus Monobond Etch & prime	Excite F DSD	Variolink II	Block to Luting cement µSBS - (n=20) Others - (n=12)	µSBS MPa Light polymerized 1200 mW/cm^2 – 20 s 24 h/ 1 y (37 °C) -Water
Silthampitag et al, 2016[44]	PEEK	SiC paper -400/2000 grit No treatment 98% H_2SO_4 -60 s Piranha solution -30 s Al_2O_3 50 µm/10 s/10 mm /0.2 MPa	Heliobond	HelioBond	Filtek Z350 XT	Block to Flowable composite resin (n=10)	SBS MPa Light polymerized 1000mW/cm^2- 40s 24h (37 °C) - Water
Şişmanoğlu et al, 2020[3]	Cera Smart Lava Ultimate Shofu Block HC Vita Enamic Vita Mark II	No treatment 9% HF acid -60 s Al_2O_3 50 µm/?? s/10 mm /0.25 MPa SiO_2-coated Al2O3 30µ m/?? s/10 mm /0.25 MPa	Clearfil Ceramic Primer Plus	Single Bond Universal	Panavia SA RelyX U200 TheraCem	Block to Luting cement (n=8)	µSBS MPa Light polymerization 1200 mW/cm^2 -20 s 5 °C-55 °C -zero and 5000 c
Tekçe et al, 2017[46]	CeraSmart Lava Ultimate Vita Enamic	SiC paper -600 grit No treatment Al_2O_3 27 µm/ 15 s/10 mm /0.25 MPa Al_2O_3 50 µm/15 s/ 10 mm /0.25 MPa SiO_2-coated Al_2O_3 30 µm/15 s/10 mm /0.25 MPa	G - Multi Primer	N/A	G-Cem LinkForce	Block to Block (n=30)	µTBS MPa Light polymerized 1200 mW/cm^2 - 4 ×80 s 24 h (37 °C) -Distilled water
Trindade et al, 2016[47]	IPS e. max CAD IPS e.max Press Vita Mark II Vita PM9 Vita VM7	10% HF 20 s (IPS e. max) or 60 s (Vita Mark II) 35% H_3PO_4 – 15 s (enamel and dentin)	Rely X Ceramic Primer	Adapter Single Bond -2 x Single Bond Universal	Rely X ARC	Block to human maxillary premolars (n=10)	µTBS MPa Light polymerized Power not displayed – 40 s 24 h (37 °C) -Distilled water 37 °C - zero and 1 200 000 c
Ustun and Ayaz, 2020[48]	Cerasmart Vita Enamic Vita Suprinity	No treatment 37% H_3PO_4 – 15 s or 30 s 5% HF 60 s or 20 s (Suprinity)	Ultradent Porcelain Silane	Single Bond Universal Adhesive	RelyX Ultimate RelyX U200	Block to human molars (n=7)	µSBS MPa Light polymerized 1000 mW/cm^2 - 4x40 s Thermocycling (half samples) 5 °C-55 °C – 5000 c
Wu et al, 2018[49]	Lava Ultimate	SiC paper -600/1000 grit No treatment SiO_2-coated Al_2O_3 30 µm/20 s/10 mm /0.25 MPa Al_2O_3 50 µm/20 s/10 mm /0.25 MPa	None Porcelain Primer	Single Bond Universal Adhesive	Rely X Veneer Rely X Unicem 2	Block to Pre-polymerized resin composite (Valux Plus) (n=15)	µSBS Light polymerized Power not displayed 6× 40 s 5 °C-55 °C – zero/10 000 c + Aging – 90 d water
Yazigi et al, 2017[50]	IPS e. max CAD	Diamond rotary instruments IDS 37% H_3PO_4 – 30 s (enamel) + 15 s (dentin) or 0s (dentin) 5% HF acid – 20 s Al_2O_3 50µm/??s/10 mm /0.20 MPa	Adhese Universal Monobond Plus	Adhese Universal	Variolink Esthetic DC	Block to human premolars (n=8)	µSBS Mpa Auto- and light polymerized Power not displayed – 20 s Aging -2 w (37 °C) -Water 5 °C-55 °C – 1 200 000 c

Al_2O_3, aluminum oxide; c, cycle; d, day; h, hour; HF, hydrofluoric acid; H_3PO_4, phosphoric acid; H_2SO_4, sulfuric acid; m, month; NaCl, sodium chloride. N/A, not applied; Scotchbond UA, scotchbond universal adhesive; SiC, silica paper abrasive; s, second; w, week; y, year; ??, not displayed.

Table 6. Resumed data extraction from the selected in vivo studies

Author, y	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Sample Pairing	Type of Test
Archibald et al, 2017[51]	IPS e.max CAD IPS e.max Press	10% HF -20 s 35% H_3PO_4 Rubber dam	Monobond S 60 s	Multilink Primer Excite DSC Scotchbond UA	Variolink II	Block to human molars 30 patients 37 restorations	Restoration assessment - modified United States Public Health Service (USPHS) criteria Two independent investigators Dropouts - 42% Participants not coming into the clinic – via telephone or email
Spitznagel et al, 2018[52]	Vita Enamic	37% H_3PO_4 40 s (enamel) + 15 s (dentin) Al_2O_3 50 µm/?? s/?? mm/?? MPa 4.9% HF -60 s Rubber dam	Syntac Primer Monobond S 60 s	Syntac Adhesive Heliobond	Variolink II	Block to human molars Prospective clinical 5-y study 48 patients 103 restorations	Block to human molars Prospective clinical 5-y study 48 patients 103 restorations
Claus-Peter, 2015[53]	IPS e.max Press	5% HF -20 s No rubber dam	Monobond Etch & Prime	Adhese Universal	Variolink Esthetic DC	Case Report	Esthetic evaluation of anterior crowns after cementation

Al_2O_3, aluminum oxide; HF, hydrofluoric acid; H_3PO_4, phosphoric acid; Scotchbond UA, scotchbond universal adhesive; s, second; m, month.

Table 7. Best and worst performance protocols for most tested CAD-CAM blocks

Author, y	CAD-CAM Block	Surface Pretreatment	Block Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Mean	SD	Il	Ul	Mechanical Test
More favorable protocol											
Liebermann, 2018[34]	Celtra Duo	SiC -1200 grit	NO	Monobond Etch & Prime	NO	Variolink Esthetic DC	35.20	3.50	31.70	38.70	TBS MPa
Tekçe, 2017[46]	CeraSmart	SiC -600 grit	Al_2O_3 50 µm	G-Multi Primer	NO	G-Cem LinkForce	58.90	9.35	47.00	68.25	µTBS MPa
Elsayed, 2017[26]	IPS e.max CAD	NO	5% HF	Monobond Plus	NO	Variolink Esthetic DC	43.10	6.10	37.00	49.20	SBS MPa
Trindade, 2016[47]	IPS e.max Press	NO	10% HF	RelyX Ceramic Primer	NO	RelyX ARC	5.40	1.30	4.10	6.70	SBS MPa
Sakrana and Özcan, 2017[42]	IPS e.max ZirCAD	SiC -400 grit	Experimental solution	Monobond Plus	NO	RelyX Ultimate	51.20	1.10	50.10	52.30	SBS MPa
Tekçe, 2017[46]	Lava Ultimate	SiC -600 grit	Al_2O_3 50 µm	G-Multi Primer	NO	G-Cem LinkForce	73.90	4.05	63.33	77.95	SBS MPa
Abdou, 2021[21]	Tetric CAD	NO	9.6% HF	Clearfil Tri-S Bond ND Quick + Porcelain Bond Activator	NO	Panavia V5	77.90	9.70	68.20	87.60	SBS MPa
Tekçe, 2017[46]	Vita Enamic	SiC -600 grit	Al_2O_3 50 µm	G-Multi Primer	NO	G-Cem LinkForce	55.20	7.53	48.20	62.73	SBS MPa
Liebermann, 2018[34]	Vita Mark II	SiC -1200 grit	9% HF	G-Multi Primer	NO	Variolink Esthetic DC	36.40	6.70	29.70	43.10	TBS MPa
Less favorable protocol											
Frankenberger, 2015[28]	Celtra Duo	SiC -600 grit	NO	NO	Prime & Bond NT + Activator	Calibra	2.40	7.20	-4.80	9.60	SBS MPa
Emsermann, 2019[27]	CeraSmart	SiC -180 grit	5% HF	Ultradent Silane	NO	RelyX Unicem 2	1.63	0.50	1.13	2.13	µSBS MPa
Elsayed, 2017[26]	IPS e.max CAD	NO	5% HF	NO	All-Bond Universal	Duo-Link Universal	0.00	0.00	0.00	0.00	SBS MPa
Trindade, 2016[47]	IPS e.max Press	NO	10% HF	RelyX Ceramic Primer	Adper Single Bond	RelyX ARC	3.60	1.30	2.30	4.90	SBS MPa
Sakrana and Özcan, 2017[42]	IPS e.max ZirCAD	SiC -400 grit	NO	Monobond Plus	NO	RelyX Ultimate	5.10	0.50	4.60	5.60	SBS MPa
Emsermann, 2019[27]	Lava Ultimate	SiC -180 grit	NO	NO	NO	RelyX Unicem 2	1.76	0.26	1.50	2.02	µSBS MPa
Ilie, 2019[29]	Tetric CAD	SiC -320 grit	NO	NO	Adhese Universal	Variolink Esthetic LC	7.71	3.99	3.72	11.70	µTBS MPa
Frankenberger, 2015[28]	Vita Enamic	SiC -600 grit	NO	NO	Prime & Bond NT + Activator	Calibra	0.00	0.00	0.00	0.00	SBS MPa
El-Damanhoury, 2017[25]	Vita Mark II	SiC -600 grit	NO	NO	NO	Multilink-N	1.82	3.18	-1.36	5.00	µTBS MPa

Al_2O_3, aluminum oxide; HF, hydrofluoric acid; il, inferior limit; ul - upper limit; NO, not used; SD, standard deviation; SiC, silica paper abrasive; µSBS, micro-shear bond strength; SBS, shear bond strength; µTBS, micro-tensile bond strength; TBS, tensile bond strength.

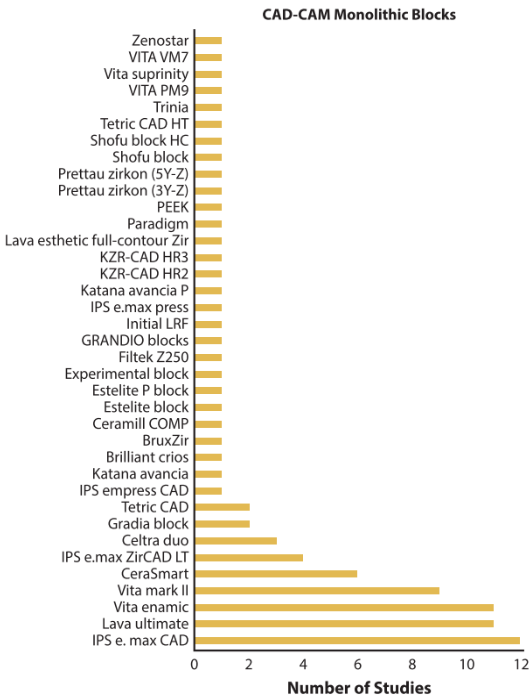

Figure 2. CAD-CAM blocks in selected studies. CAD-CAM, computer-aided design and computer-aided manufacturing.

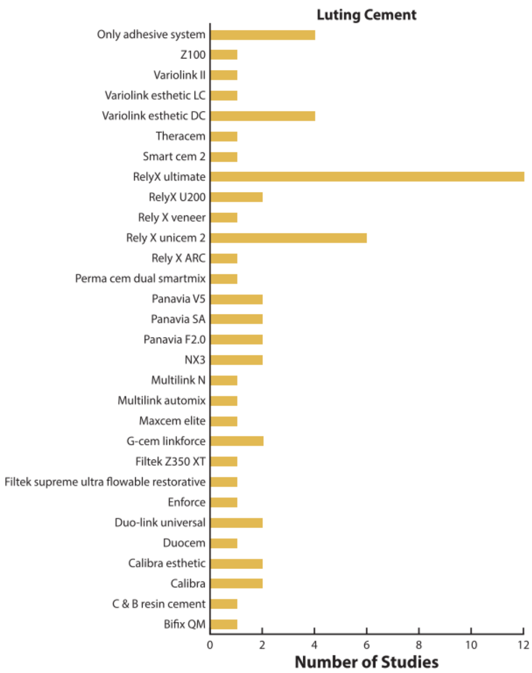

Figure 3. Luting cement in selected studies.

Among the most in vitro tested blocks, IPS e.max CAD (lithium disilicate) >Vita Enamic (hybrid ceramic with a dual ceramic-polymer network structure) =LAVA Ultimate (80% nanoceramic resin) >Vita Mark II (reinforced nanoleucite crystals feldspathic porcelain), none require high-temperature crystallization, with no need for laboratory processing and facilitating in-office handling. Some tested in vitro protocols exposed dental laboratory technicians, clinicians, or patients to risk (high temperature, acids, or both), despite inducing the best mechanical performance for a specific material.[17,42] This entails pertinent guidelines for research with humans,[22,51] possibly discouraging RCTs, a possible reason for finding only 2 observational studies.

Tests assessing strength varied, consistent with the literature,[29] as did the protocols simulating aging or bonding failure. The choice of the best CAD-CAM block-adhesive system pair for clinical use was complex, as referred to in 1 article.[48] TBS and SBS tests, popular for 7- to 28-mm^2 bonded areas, are larger than intraoral dimensions.[3] µSBS and µTBS tests, which improve factors related to cohesive failures in areas larger than 2 square millimeters[3] and lower failure coefficients,[13,22,33] were found at most. One study used SBS and µTBS

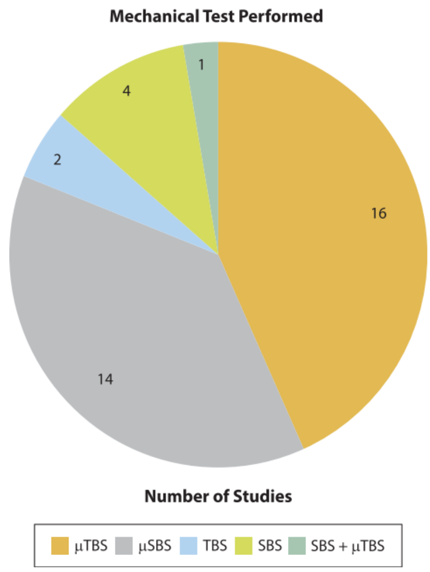

Figure 4. Number of studies using each type of test. µSBS, microshear bond strength; µTBS, microtensile bond strength; SBS, shear bond strength; TBS, tensile bond strength.

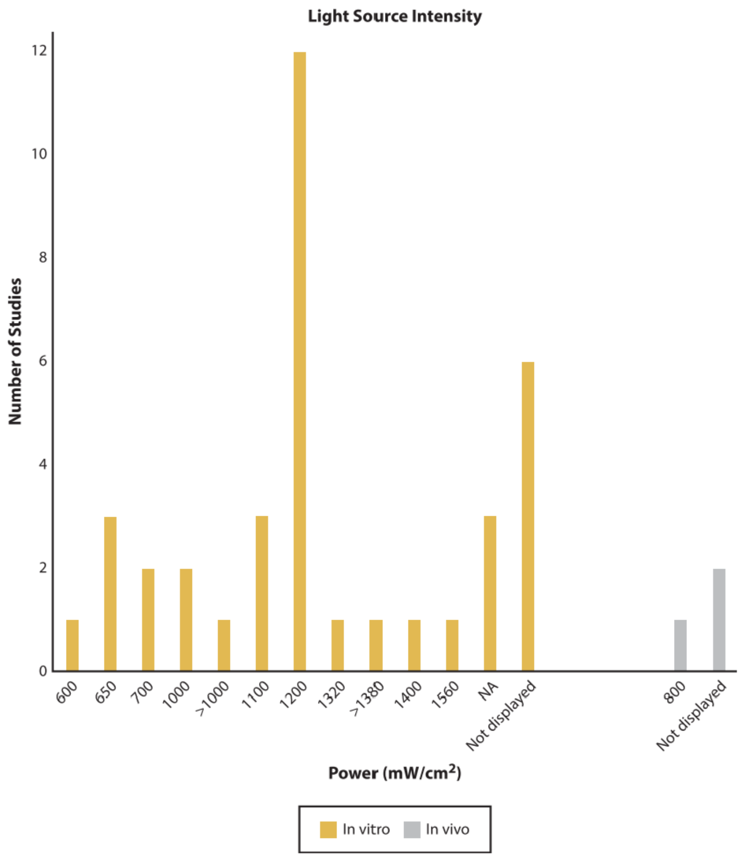

Figure 5. Light source intensity used for polymerization.

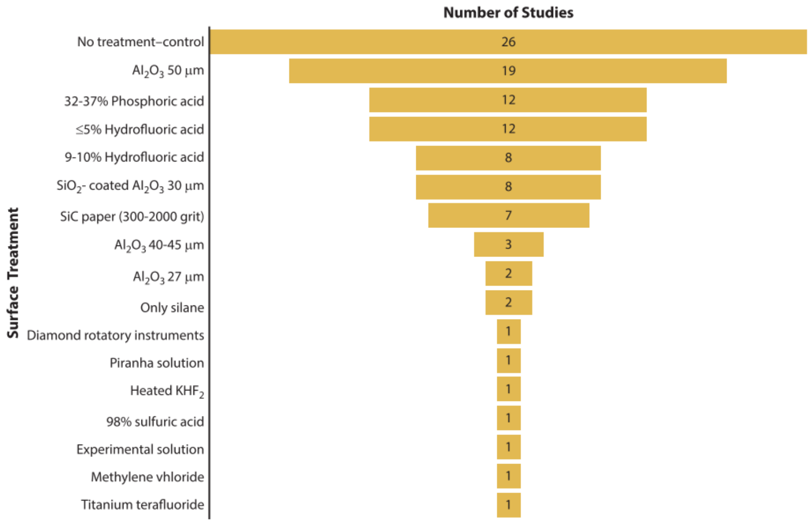

Figure 6. Surface treatments in selected studies.

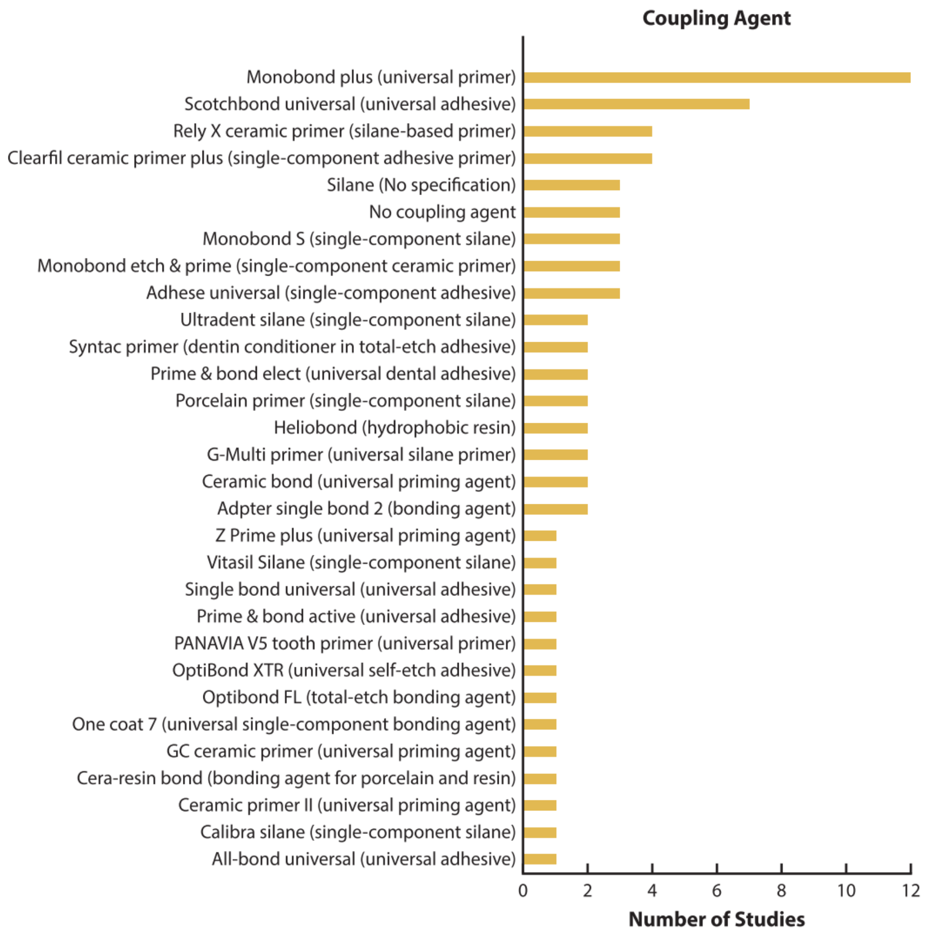

Figure 7. Coupling agents in selected studies.

sequentially,[22] while the others used SBS,[25,29,40,44] TBS,[34,35] μSBS,[3,11,13,16,23,24,27,31,38,43,45,48-50] or μTBS [18,21,26,28,30,32,33,36,37,39,41,42,46,47] tests. The option for a specific test was more likely a researcher's preference rather than a universal analysis standard.[33] No temporal association was found between the type of test and year of publication, neither with the material tested nor the paired adhered materials. Tests with human teeth showed a lower difference between the means (Fig. 11) with the worst adhesive performances. The highest absolute values were more dependent on the paired joint substrates and tested protocols than on the test performed.

Protocols simulating aging or material fatigue differed among studies concerning thermocycling, ranging from 5000[23,25] to 1 200 000[47] cycles, with different moisture and temperature conditions for the same test. Specimens were kept in water, not reproducing the dynamic oral environment (temperature, saliva baths, occlusal loads, or eventual parafunctional habits).[32,34,46,48] Storage in nonspecified water, deionized water, distilled water, or saline solution was identified. Initial storage was usually 24 hours, except in 4 studies (30 minutes,[37] 1 hour,[38] 3 days,[39] and 2 weeks[50]). If the effect of aging was a research purpose, subsequent storage varied from 30 days[26,33,39] to 1 year,[13,45] with intermediate intervals of 3,[33] 5,[26,39] and 6 months[16,27,49] A convergence for the objective temperature (37 °C) was found. Wavelengths in light-polymerizing protocols were 650 to 1560 mW/cm^2 (1200 mW/cm^2 in approx. 67.5% of the studies), and polymerization times were 20 seconds[11] to 400

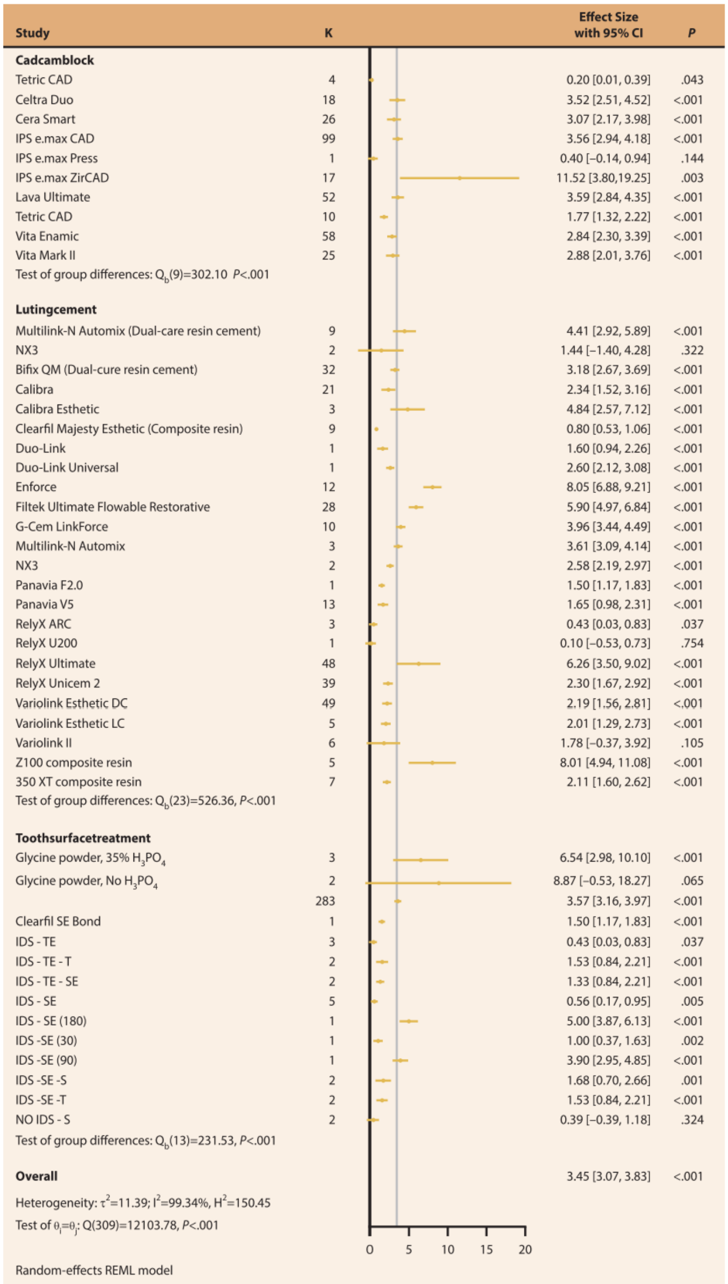

Figure 8. Forest plot summarizing effect size between control protocols and all other tested protocols by CAD-CAM block, luting cement, and tooth surface treatment. CAD-CAM, computer-aided design and computer-aided manufacturing.

Study	Treatment N	Treatment Mean	Treatment SD	Control N	Control Mean	Control SD	Best vs Worst with 95% CI	Weight (%)
Block								
Tekçe, 2017 Vita Enamic	30	55.2	7.53	30	21.5	4.8	5.34 [4.24, 6.43]	1.55
Elsaka, 2020 Vita Enamic	30	29.17	2.79	30	19.36	3.41	3.15 [2.38, 3.91]	3.17
Abdou, 2021 Tetric CAD	6	77.9	9.7	6	46.5	7.8	3.57 [1.64, 5.50]	0.50
Elsaka, 2020 Leva Ultimate	30	27.85	3.47	30	12.12	2.19	5.42 [4.31, 6.53]	1.51
Elsaka, 2020 Vita Enamic (5,000 cycles)	30	25.64	3.01	30	19.44	3.06	2.04 [1.41, 2.67]	4.70
Elsaka, 2020 Lava Ultimate (5,000 cycles)	30	24.15	2.73	30	9.33	1.5	6.73 [5.40, 8.05]	1.06
Takçe, 2017 Cera Smart	30	58.9	9.35	30	13.95	7.08	5.42 [4.31, 6.53]	1.51
Tekçe, 2017 Lava Ultimate	30	73.9	4.05	30	15.4	2.9	16.61 [13.54, 19.67]	0.20
Abdou, 2021 Vita Enamic	6	47.7	8.3	6	38.8	12.8	0.83 [−0.36, 2.01]	1.31
Heterogeneity: I^2=95.20%, H^2=20.82							3.71 [3.36, 4.05]	
Test of θ_i=θ_j: Q(8)=166.60, P<.001								
Bovine Tooth								
Ceci, 2015 Lava Ultimate	5	17.88	1.44	5	3.3	.39	13.82 [6.94, 20.71]	0.04
Heterogeneity: I^2=100.00%, H^2=1.00							13.82 [6.94, 20.71]	
Test of θ_i=θ_j: Q(8)=−0.00, P<.001								
Composite Resin								
Demirel, 2019 Cera Smart	10	19.32	9.46	10	10.31	5.9	1.14 [0.19, 2.10]	2.04
Demirel, 2019 Lava Ultimate	10	18.17	10.31	10	12.23	6.92	0.68 [−0.23, 1.58]	2.27
Kalavacharla, 2015 IPS e.max CAD	10	40.47	4.2	10	1.82	2	11.75 [7.81, 15.69]	0.12
Demirel, 2019 Vita Enamic	10	15.58	6.94	10	5.94	3.86	1.72 [0.68, 2.76]	1.71
Dos Santos, 2019 IPS e.max ZirCAD	10	37.12	9.42	10	13.69	3.47	3.30 [1.91, 4.69]	0.96
Sakraana and Özcan, 2017 IPS e.max ZirCAD	10	51.2	1.1	10	17.4	1.1	30.73 [20.65, 40.80]	0.02
Sakraana and Özcan, 2017 IPS e.max ZirCAD (7,500 cycles)	10	49.5	1	10	5.1	5	56.16 [37.80, 74.53]	0.01
Heterogeneity: I^2=94.12%, H^2=17.00							1.72 [1.21, 2.23]	
Test of θ_i=θ_j: Q(6)=102.02, P<.001								
Flowable Composite Resin								
Passia, 2015 IPS e.max CAD (37 500 cycles)	8	22.4	8.5	8	0	.0001	3.73 [2.03, 5.42]	0.65
Passia, 2015 IPS e.max CAD	8	38.5	6.2	8	17.2	4.5	3.93 [2.18, 5.69]	0.60
Passia, 2015 IPS e.max CAD (7 500 cycles)	8	22.9	9.7	8	0	.5	3.33 [1.76, 4.91]	0.75
Heterogeneity: I^2 = 0.00%, H^2=1.00							3.64 [2.68, 4.61]	
Test of θ_i=θ_j: Q(2)=0.26, P=.88								
Human Molars								
Ustun and Ayaz, 2020 cera Smart (5 000 cycles)	7	7.57	.37	7	5.62	.29	5.87 [3.30, 8.44]	0.28
Ustun and Ayaz, 2020 Vita Enamic (5 000 cycles)	7	6.37	.33	7	4.59	.41	4.78 [2.60, 6.96]	0.39
Ustun and Ayaz, 2020 Vita Enamic	7	8.54	.31	7	7.14	.45	3.62 [1.83, 5.41]	0.58
Ustun and Ayaz, 2020 Cera Smart	7	9.89	.32	7	7.48	.32	7.53 [4.34, 10.72]	0.18
Roperto, 2016 Vita Mark II	30	17.68	2.71	30	6.48	3.1	3.85 [2.98, 4.71]	2.49
Ishii, 2017 Vita Enamic	12	15.5	2.2	12	15.2	3.3	0.11 [−0.69, 0.91]	2.89
Kassem, 2020 Cera Smart (150 000 cycles)	8	45.7	4.6	8	43.4	5.5	0.45 [−0.54, 1.45]	1.88
Ishii, 2017 Lava Ultimate	12	26.6	6.5	12	21.2	6.1	0.86 [0.02, 1.70]	2.63
Ishii, 2017 Vita Mark II	12	5.1	3.9	12	3.5	1.6	0.54 [−0.28, 1.35]	2.79
Murata, 2018 Vita Mark II (20 000 cycles)	8	12.6	2	8	4.6	1.1	4.96 [2.88, 7.04]	0.43
Kassem, 2020 Cera Smart	8	48.2	7.1	8	46.6	6.4	0.24 [−0.75, 1.22]	1.92
Heterogeneity: I^2=90.71%, H^2=10.77							1.46 [1.13, 1.80]	
Test of θ_i−θ_j: Q(10)−107.66, P<.001								
Human Premolars								
Yazigi, 2017 IPS e.max CAD	8	18.44	3.57	8	11.22	3.36	2.08 [0.84, 3.33]	1.19
Yazigi, 2017 IPS e.max CAD (1 200 000 cycles)	8	18.33	5.7	8	12.75	4.27	1.11 [0.05, 2.17]	1.64
Trindade, 2016 IPS e.max Press (1 200 000 cycles)	10	3.6	1.3	10	5.4	1.3	−1.38 [−2.37, −0.40]	1.91
Trindade, 2016 Vita Mark II (1 200 000 cycles)	10	9.7	1.8	10	8.2	1.9	0.81 [−0.11, 1.73]	2.21
Trindade, 2016 IPS e.max CAD (1 200 000 cycles)	10	2.6	1.6	10	2.2	1.4	0.27 [−0.61, 1.15]	2.39
Heterogeneity: I^2=81.91%, H^2=5.53							0.44 [−0.01, 0.88]	
Test of θ_i=θ_j: Q(4)=22.11, P<.001								
Luting Cement								
El-Damanhoury, 2017 Vita Mark II	10	27.97	8.38	10	1.82	3.18	4.13 [2.52, 5.73]	0.72
Ilie, 2019 Tetric CAD (10 000 cycles)	20	16.91	3.62	20	7.71	3.99	2.42 [1.59, 3.24]	2.73
El-Damanhoury, 2017 Vita Enamic	10	25.96	11.49	10	3.43	4.06	2.61 [1.39, 3.84]	1.24
El-Damanhoury, 2017 IPS e.max CAD	10	37.6	10.68	10	1.62	2	4.68 [2.92, 6.45]	0.60
Ilie, 2019 Tetric CAD	20	27.77	8.87	20	16.86	4.89	1.52 [0.82, 2.23]	3.70
Lümkemann, 2018 IPS e.max CAD (20 000 cycles)	18	35.8	7.5	18	34	9	0.22 [−0.44, 0.87]	4.32
Liebermann, 2018 IPS e.max CAD (20 000 cycles)	18	34	8.2	18	1.3	5.4	4.71 [3.41, 6.01]	1.10
Lümkemann, 2018 Tetric CAD (20 000 cycles)	18	33.3	5.7	18	30.8	7.7	0.37 [−0.29, 1.03]	4.27
Lümkemann, 2018 IPS e.max ZirCAD (20 000 cycles)	18	39.6	4.7	18	37.5	9.2	0.29 [−0.37, 0.94]	4.30
Liebermann, 2018 Celtra DUO (20 000 cycles)	18	35.2	3.5	18	2.7	3.8	8.90 [6.68, 11.11]	0.38
Liebermann, 2018 Vita Mark II (20 000 cycles)	18	36.4	8.2	18	10.2	8.4	3.16 [2.16, 4.15]	1.87
Şişmanoğlu, 2020 Vita Mark II (5 000 cycles)	8	28.31	1.38	8	6.29	1.25	16.72 [10.45, 23.00]	0.05
Emsermann, 2019 Cera Smart	20	4.27	.5	20	1.63	.5	5.28 [3.94, 6.62]	1.03
Şişmanoğlu, 2020 Vita Enamic (5 000 cycles)	8	32.34	2.72	8	10.97	1.56	9.64 [5.94, 13.34]	0.14
Murilo Gómez, 2017 IPS e.max CAD	18	27.2	3.1	18	18.8	3	2.75 [1.83, 3.68]	2.17
Şişmanoğlu, 2020 Lava Ultimate (5 000 cycles)	8	34.01	2.33	8	12.22	2.51	9.00 [5.52, 12.47]	0.15
Cardenas, 2017 IPS e.max CAD	10	32.1	1.7	10	12.5	2.5	9.17 [6.05, 12.29]	0.19
Murilo Gómez, 2017 IPS e.max CAD (180 days)	18	22.2	5.4	18	15.7	5.8	1.16 [0.45, 1.87]	3.69
Emsermann, 2019 Vita Enamic	20	7.1	.77	20	2.82	.63	6.08 [4.58, 7.59]	0.82
Emsermann, 2019 Lava Ultimate	20	6.63	.97	20	1.76	.26	6.86 [5.20, 8.52]	0.67
Siqueira, 2019 IPS e.max CAD (365 days)	10	30.05	2.3	10	16.86	.7	7.76 [5.08, 10.44]	0.26
Siqueira, 2019 IPS e.max CAD	10	30.97	.5	10	29.27	2.3	1.02 [0.08, 1.96]	2.11
Şişmanoğlu, 2020 Cera Smart (5 000 cycles)	8	32.87	3.56	8	15.71	2.24	5.77 [3.42, 8.12]	0.34
Elsayed, 2017 IPS e.max CAD (37 500 cycles)	20	32	11.7	20	0	.0001	3.87 [2.80, 4.94]	1.63
Frankenberger, 2015 Vita Enamic	24	23.4	5	24	0	.0001	6.62 [5.15, 8.08]	0.86
Elsayed, 2017 IPS e.max CAD	20	43.1	6.1	20	13.6	2.7	6.25 [4.72, 7.79]	0.79
Frankenberger, 2015 Lava Ultimate	24	17.9	4.5	24	4.2	9.1	1.91 [1.22, 2.60]	3.93
Frankenberger, 2015 IPS e.max CAD	24	26.3	7.7	24	3.5	8.3	2.85 [2.04, 3.66]	2.82
Frankenberger, 2015 Celtra Duo	24	31.2	7.9	24	2.4	7.2	3.81 [2.85, 4.77]	2.00
Elsayed, 2017 IPS e.max CAD (7,500 cycles)	20	35.2	7.2	20	0	.0001	6.91 [5.24, 8.59]	0.66
Heterogeneity: I^2=93.76%; H^2=16.02							2.44 [2.24, 2.63]	
Test of θ_i=θ_j: Q(29)=464.65, P<.001								
Overall								
Heterogeneity: I^2=93.77%; H^2=16.04							2.26 [2.13, 2.40]	
Test of θ_i=θ_j: Q(65)=1042.70, P<.001								
Test of group differences: Q_b(6)=179.40, P<.001								

Fixed-effects inverse-variance model

Figure 9. Forest plot summarizing effect size by joint substrate.

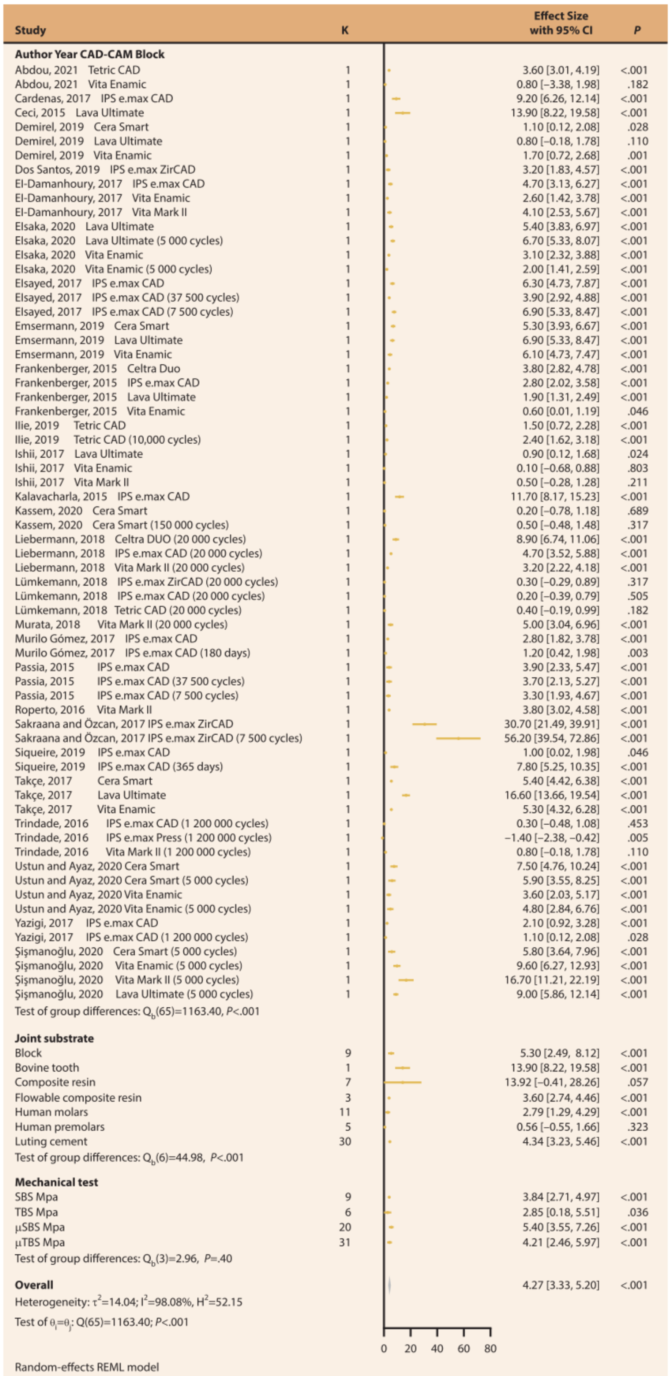

Figure 10. Forest plot summarizing effect size by joint substrate, mechanical test, and bonding protocol by study and most tested blocks.

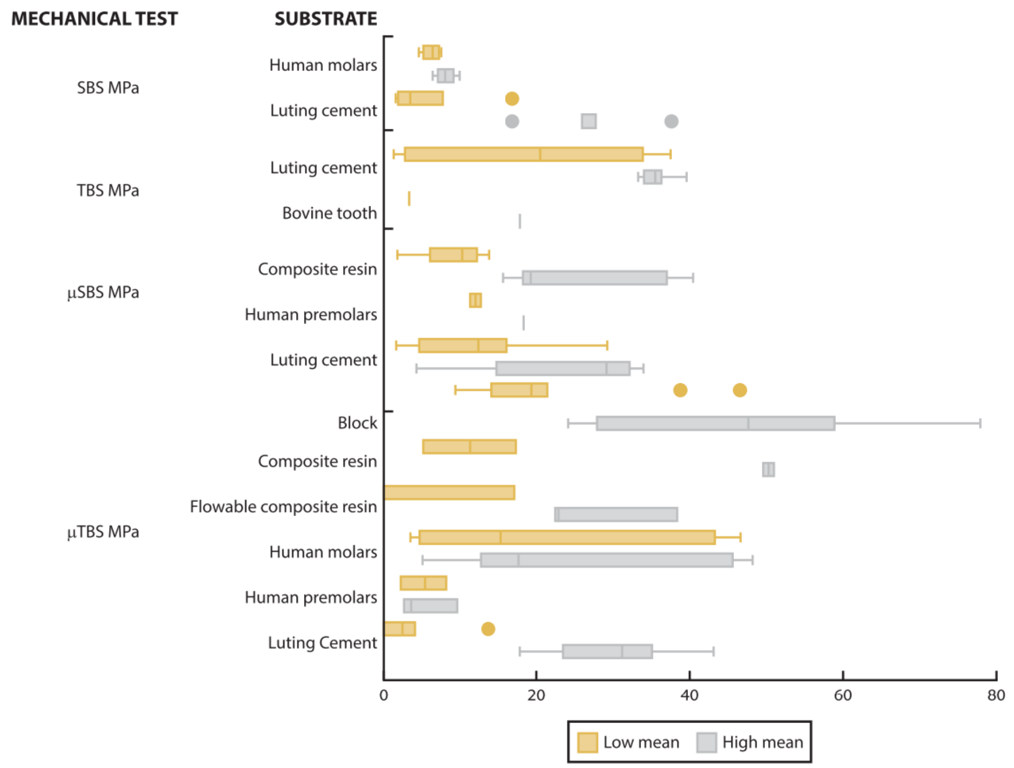

Figure 11. Means by kind of test and substrate for mainly used blocks. µSBS, microshear bond strength; µTBS, microtensile bond strength; SBS, shear bond strength; TBS, tensile bond strength.

seconds,[6] variations that confuse clinicians are clinically questionable in terms of time expenditure (7 minutes per tooth) and potential pulp injury.[57]

The number of available materials makes it impossible to test all of them at the same time, forcing researchers to restrict testing, a limitation because, even though a dual-polymerizing composite resin cement is the standard for adhesive cementation, different brands have different properties and components.[31,34,45] These differences were the main reason for subgrouping the cements and CAD-CAM blocks by the authors. Researchers select some materials over others, reflecting the choice for more user-friendly materials. The most tested luting cement was Rely X Ultimate,[3,6,11,13,16,18,23,25-28,30,31,33,36,37,39,42,46,48,50,52,53] probably because it combines dual polymerization with the possibility of total-etch, selective-etch, or self-etch adhesive strategies. However, the chosen materials may have been conditioned by research support from the manufacturer or by the clinical preference of the researcher.

CONCLUSIONS

Based on the findings of this systematic integrative review and meta-analysis, the following conclusions were drawn:

1. Despite the objective standards for the individual in vitro tests, a lack of standardization for each technical step was evident.
2. Some tested protocols were more efficient than others for each CAD-CAM block.
3. The number of protocols found makes selecting the most suitable protocol for each block or clinical situation difficult for the clinician.
4. Randomized clinical trials were nonexistent, and well-documented clinical situations were scarce, making the inference of direct application of in vitro findings into clinical practice impossible.
5. Based on the data collected, a rapid and efficient translation from in vitro scientific evidence to clinical practice is a complex and time-consuming task.

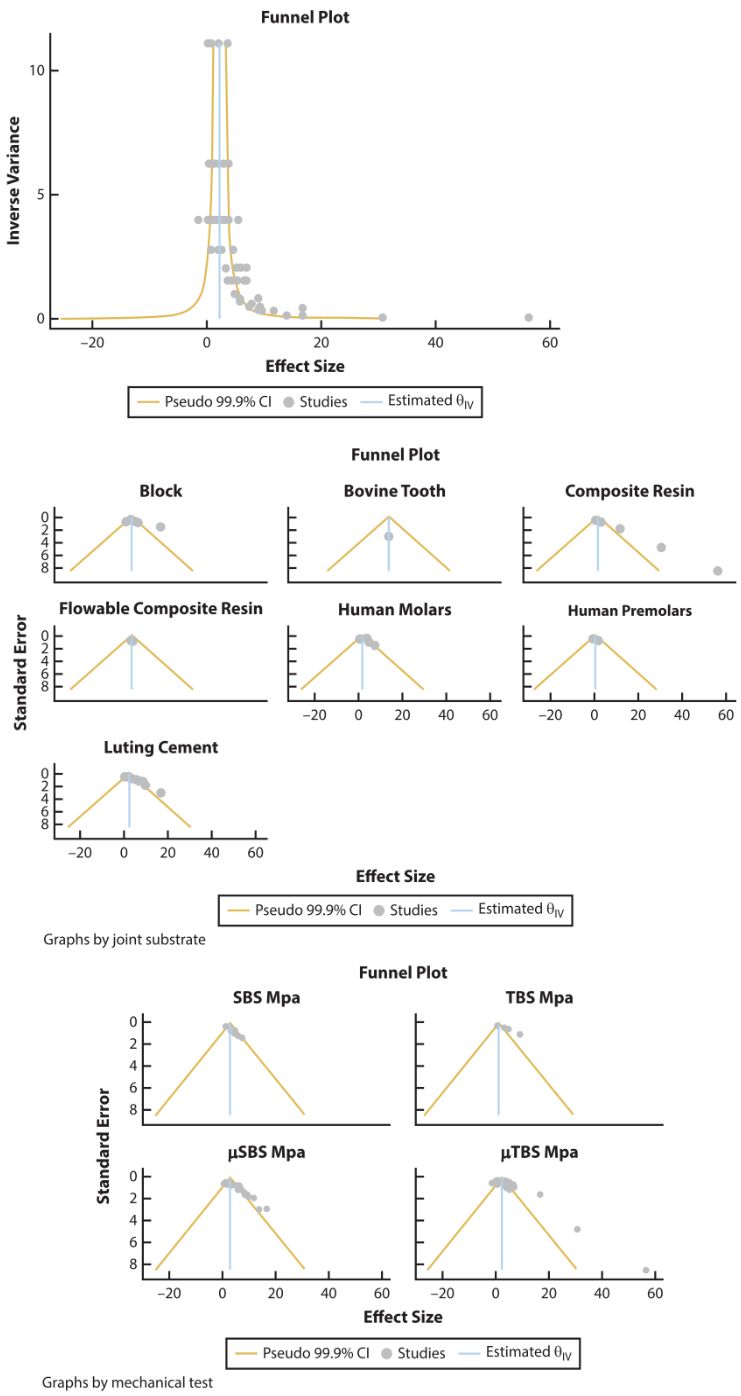

Figure 12. Funnel plots of publication bias of all selected publications and filtered by joint substrate and mechanical test.

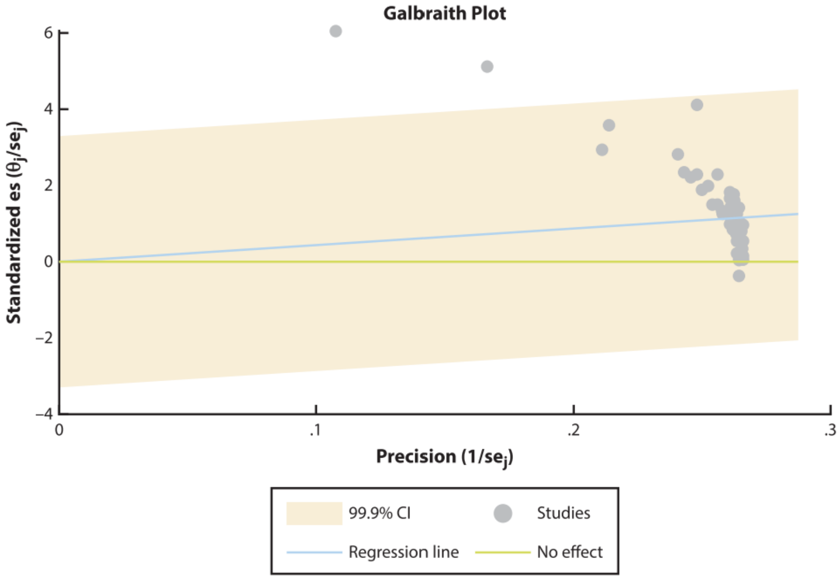

Figure 13. Heterogeneity assessment among effect sizes.

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materials

MDPI

Systematic Review

Effectiveness of Self-Adhesive Resin Luting Cement in CAD-CAM Blocks—A Systematic Review and Meta-Analysis

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Abstract: Self-adhesive resin cements (SARCs) are used because of their mechanical properties, ease of cementation protocols, and lack of requirements for acid conditioning or adhesive systems. SARCs are generally dual-cured, photoactivated, and self-cured, with a slight increase in acidic pH, allowing self-adhesiveness and increasing resistance to hydrolysis. This systematic review assessed the adhesive strength of SARC systems luted to different substrates and computer-aided design and manufacturing (CAD/CAM) ceramic blocks. The PubMed/MedLine and Science Direct databases were searched using the Boolean formula [((dental or tooth) AND (self-adhesive) AND (luting or cement) AND CAD-CAM) NOT (endodontics or implants)]. Of the 199 articles obtained, 31 were selected for the quality assessment. Lava Ultimate (resin matrix filled with nanoceramic) and Vita Enamic (polymer-infiltrated ceramic) blocks were the most tested. Rely X Unicem 2 was the most tested resin cement, followed by Rely X Unicem > Ultimate > U200, and μTBS was the test most used. The meta-analysis confirmed the substrate-dependent adhesive strength of SARCs, with significant differences between them and between SARCs and conventional resin-based adhesive cement ($\alpha < 0.05$). SARCs are promising. However, one must be aware of the differences in the adhesive strengths. An appropriate combination of materials must be considered to improve the durability and stability of restorations.

Keywords: dental; tooth; self-adhesive; luting; cement; CAD-CAM; monolithic ceramics; blocks

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1. Introduction

CAD-CAM technology in dental medicine is developing, allowing protocol standardization and a predictable quality of dental restorations while reducing the production price [1,2], aiming to deliver materials at their highest quality [3], and enhancing the outgrowth of highly esthetic and functional restorative materials [4–6]. This technology has boosted impression and casting procedures [6–9], supplying easier and quicker indirect restorations, frequently without the requirement for provisional restorations or dental laboratories, allowing single-visit [4,8,9] inlays, onlays, veneers, or even full-contour crowns fabricated with several alternative materials with high survival rates [10–12]. Candidate materials may incorporate lithium disilicate glass-ceramic, leucite-reinforced glass-ceramic, feldspathic ceramic, zirconia, resin-matrix composites, polymer-infiltrated ceramic, or titanium [1,13]. Rehabilitation with CAD-CAM materials is becoming a standard dental technique due to high-tech digital technology based on image-capturing scanner devices, software, and integrated CAD-CAM systems [13,14].

Adhesive strength, or adhesive efficacy, refers to the ability of an adhesive to bond two surfaces together and resist separation. It measures the force required to pull the two surfaces apart once they have been joined by the adhesive. It depends on various factors, such as the type of adhesive, the nature of the surfaces being bonded, the conditions under which the adhesive is applied, and the time allowed for the adhesive to cure or dry. Luting cement adhesive strength is the ability of dental cement to bond to tooth structure or other dental materials effectively [15,16]. For each type of material, a previous treatment of the surface to be adhered to is required before applying the luting cement [13,17,18]. Conventionally, for resin-based materials (Cerasmart, Estelite, HZR-CAD HR2, Lava Ultimate, Katana Avencia, Paradigm, Shofu Block HC) and polymer infiltrated ceramic (such as Vita Enamic), aluminum oxide sandblasting (SB) or etching with hydrofluoric acid (HF), both complemented by the application of silane coupling agent, is recommended [17]. For all glass ceramics, etching with hydrofluoric acid complemented by silane is the standard surface treatment. However, for feldspathic- and leucite-reinforced ceramics (IPS Empress CAD, IPS. e max CAD, IPS. e max Press, Vita Mark II), HF 5% between 30 and 120 s is recommended. At the same time, for lithium disilicate glass-ceramic (Celtra Duo, Vita Suprinity), it is not wise to use HF concentrations greater than 4.9% for 20 s [19]. Materials that contain methyl methacrylate (MMA) improve the bonding of CAD/CAM poly(methyl methacrylate) (PMMA) resin materials (artBloc Temp) [17].

When adhering CAD-CAM ceramic to tooth substrates, luting cement is crucial for clinical success and restoration longevity, and adhesive luting is more favorable than non-adhesive luting, except in the case of zirconia [8,20,21]. Adhesive luting cement is categorized according to the adhesion strategy as a conventional multi-step resin composite cement combined with an etch-and-rinse or self-adhesive system, and as self-adhesive resin cement (SARC) [22,23].

Introduced at the beginning of the 21st century as a revolutionary cement with a time-saving clinical protocol, SARC was designed to be an easier-to-handle cement [24]. In the SARC protocol, surface treatment of the joint substrates is not required [25,26] because it allows bonding to an unconditioned tooth surface, without pretreatment with an acid or adhesive, theoretically with a similar adhesive strength as that of the established conventional multi-step resin cement [27]. However, for better adhesion, mild acids can be used to remove or modify the smear layer [28]. The adhesive strength was reported to be lower in systems where the smear layer was modified rather than removed [27]. In addition, air polishing devices (sandblasting), by increasing the roughness of hard dental tissues and restorative materials, have been reported to increase the adhesive strength of an SARC [9].

Unlike the first generation of SARCs that demand surface treatment by sandblasting and silanization, the silane-containing SARCs, recently released on the market, do not need the silanization step [25]. The chemical composition of these SARCs is based on methacrylate monomers modified by carboxylic or phosphoric acid groups, simultaneously demineralizing and infiltrating dentin and enamel without the need for separate etching and bonding steps, forming micromechanical interlocking and chemical bonding by interaction with the calcium ions of the tooth substrate [23]. After paste mixing, the phosphoric acid groups react with the hard tissue of the tooth and basic fillers in the luting material (cement reaction) to form a bond. In parallel with the cement reaction, the polymerization of methacrylate monomers is initiated (radical polymerization). Meanwhile, the acid groups are neutralized, turning the material's behavior from hydrophilic to hydrophobic [24,26,29].

Despite being more straightforward, professionals must know that problems can occur during cementation with SARC. Lack of polymerization efficiency, with the potential release of unreacted cytotoxic and genotoxic monomers [30], induces expansion of the cement layer, with polymerization shrinkage strain and high stresses caused by hygroscopic expansion, with possible crack formation and restoration failure [26,28]. An evenly distributed cement layer with low internal gap values is essential for correct seating and better mechanical properties, but also for a low-space volume of the cement and porosities inside the luting agent [5]. Factors such as the cement mixing method or the particle size might amplify the formation of porosities [5]. Furthermore, differences in humidity, pH, and oral cavity temperature cause changes in dental materials [31]. SARCs exhibit good biocompatibility and marginal integrity, low microleakage [6], mechanical quality, and esthetic properties, being the most commonly used cements for the bonding of a restoration [30]. The adhesive strength of CAD-CAM ceramics to tooth substrates also depends on the type of ceramic, resin-matrix cement, the functional monomer used, and patient-related factors such as dentin thickness, occlusal loading, dental age, and proper oral hygiene [27].

Considering the existence of different adhesive strategies and that SARCs do not require additional steps for the adhesion of CAD-CAM restorations, it is necessary to clarify the adhesive strength of SARCs when cementing CAD-CAM ceramic blocks to tooth substrates. In parallel, it is also pertinent to assess the adhesive strength of each SARC when cementing different CAD-CAM ceramic blocks and compare their adhesive strength with conventional multi-step resin cements.

The first null hypothesis was that no differences exist in the adhesive strength between the self-adhesive resin-matrix cement systems used to lute CAD-CAM ceramic blocks. The second null hypothesis was that no differences exist between the self-adhesive resin-matrix cement and conventional resin-matrix cement used for luting CAD-CAM ceramic blocks.

2. Materials and Methods

The review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 recommendations [32]. The population, intervention, comparison, and outcome (PICO) question was: "Are the self-adhesive resin-matrix cements efficient in luting CAD-CAM blocks?" The CAD-CAM blocks constituted the population. The intervention was defined as the cementation of blocks to dental and non-dental substrates. A comparison was made between each self-adhesive luting cement to determine intra- and interstudy differences in mechanical performance and between them and conventional resin-matrix luting cement. The adhesive strength was defined as the outcome.

2.1. Databases and Search Strategy

Bibliographic research was carried out in MedLine/PubMed and Science Direct databases with the keywords conjugated in the Boolean search formula: ("dental" [All Fields] OR "tooth" [MeSH Terms]) AND (("self-adhesive" [All Fields]) AND ("luting" [All Fields] or "cement" [All Fields])) AND "CAD-CAM" [All Fields] NOT ("endodontics" [MeSH Terms] OR "implants" [All Fields]) and in Science Direct the keywords combined in the formula ("dental" or "tooth") AND ("self-adhesive") AND ("luting" or "cement")) AND "CAD-CAM") NOT ("endodontics" or "implants"), from 1 January 2012 to 31 July 2022, and again revised on 10 January 2023, for possible new entries.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria were English language, accessible full-text research articles published in the last ten years, evaluation of adhesion strength between resin cement and dental and non-dental substrates, studies assessing microshear bond strength (μSBS), macroshear bond strength (SBS), microtensile bond strength (μTBS), and macrotensile bond strength (TBS) tests, and marginal parameter evaluation.

The exclusion criteria were non-CAD-CAM ceramic blocks, absence of bonding strength evaluation, data not presented in MPa or without a normal distribution, clinical trials, case reports, case series, pilot studies, encyclopedia articles, and articles published before 2012.

Preliminary removal of duplicate articles was performed using a citation manager (EndNote X9 Windows; Clarivate). Articles were then filtered by title, abstract, and complete reading in agreement with the PRISMA Statement.

Two investigators (M.J.C.L. and T.L.V.) independently selected each pertinent article for a detailed reading. A third investigator (T.P.) resolved any disagreements.

Additional research was conducted manually, pairing each word with the words self-adhesive and universal adhesives to identify relevant literature reviews, systematic reviews related to the subject, or other studies indirectly related to the topic to allow comparisons or enrich the introduction and discussion sections.

2.3. Quality Assessment Protocol

The selected articles were included in this systematic review and subjected to quality assessment to determine the risk of bias (BIAS), which was calculated according to the following criteria: random distribution of the specimen, blind sampling by the operator, single operator, standardization of the specimen, control group, fractographic analysis, respect for the manufacturer's instructions, compliance with international standards (ISO), sample size calculation, and statistical analysis quality.

The study's publication date and the publication's quotation by date in the SRJ score (Q_1–Q_4) were also analyzed. Qualitative analysis of the risk of bias assessment was performed by individually scoring the ten selected parameters using the following criteria: (0) clearly mentioned, (1) present but not accurately mentioned, and (2) not mentioned. Global scoring was categorized as low (0–4), medium (5–12), high (13–17), or very high (18–20) risk of bias.

2.4. Data Extraction Workflow

Data extraction was performed, and the data were condensed into tables according to the item's author, year of publication, CAD-CAM material, sample size, pairing (luted substrate), type of test performed, surface treatment, coupling agent used, adhesive system used, and luting cement tested. The mean and standard deviation of the bond strength were recorded in MPa, and the values for marginal adaptation were registered for statistical treatment.

2.5. Meta-Analysis

A meta-analysis of the adhesive strategies for each luting cement brand was conducted using a software program (Stata v17.0; StataCorp, Lakeway, TX, USA). Subgroup analyses assessed the different types of surface treatment methods, adhesive joint substrates, and mechanical tests. For all studies that evaluated more than one type of CAD-CAM block or more than one surface treatment method, each type of material or treatment method was considered independently.

Statistical heterogeneity was determined using the I^2 test ($\alpha = 0.05$). A meta-analysis was conducted by the author and the CAD-CAM block to determine intrastudy heterogeneity and protocol splitting by efficiency after calculating the difference between means and effect size ($\alpha = 0.05$; 95% CI; Z-value 1.96) (Table S1). Funnel and Galbraith's plots assessed publication bias and heterogeneity (random-effects model; $\alpha = 0.01$; 99.9% CI; Z-value 2.58).

3. Results

3.1. General Aspects

The search retrieved 199 articles [Medline/PubMed (93) and ScienceDirect (106)]. One article was immediately excluded based on language, and 50 were duplicate publications. Seventy-seven articles were removed by reading the titles and abstracts, and 42 were removed after complete reading. The remaining 29 articles [1–10,14,22,25–28,31,33–44] were selected for the quality analysis. Manual research also retrieved three studies [30,45,46], three randomized clinical trials [24,47,48], six reviews [15,23,29,49–51], and three meta-analyses [11,12,20], which were used to broaden the introduction and discussion sessions. The selection process agreed with the PRISMA Statement, as shown in Figure 1.

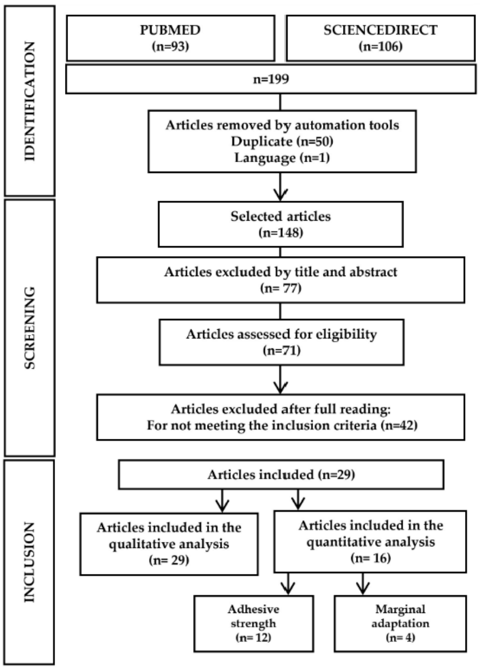

Figure 1. Flow diagram of study selection according to the PRISMA statement.

3.2. BIAS Risk Assessment

Qualitative analysis for risk of bias assessment (Table 1) revealed one low-risk [34] (3.45%) and 30 medium-risk of bias (96.55%) articles. Transversal factors for lower scores were the absence of operator blindness (referred to in two articles [3,34] (6.9%)) and no reference to a single operator (referred to in five studies [6,9,33,34] (13.79%)).

Table 1. BIAS risk assessment and SJR scoring.

Study	Abdou et al. (2021) [7]	Albelasy et al. (2021) [31]	Ali et al. (2012) [33]	Augusti et al. (2020) [34]	Bayazit et al. (2019) [8]	Ceci et al. (2016) [9]	Dauti et al. (2020) [5]	Elsaka et al. (2014) [35]	Ender et al. (2016) [3]	Melo Freire et al. (2017) [22]	Han et al. (2020) [28]	Higashi et al. (2016) [1]	Kawaguchi et al. (2016) [10]	Kirsten et al. (2018) [26]	Liebermann et al. (2013) [2]	Magne et al. (2015) [36]	Malysa et al. (2022) [37]	Nagasawa et al. (2021) [38]	Nagasawa et al. (2022) [14]	Nakamura et al. (2016) [39]	Oda et al. (2021) [25]	Peumans et al. (2016) [40]	Poggio et al. (2016) [6]	Preis et al. (2015) [4]	Sorrentino et al. (2016) [42]	Takahashi et al. (2022) [43]	Ustun et al. (2021) [27]	Zahoui et al. (2020) [44]	Zhang et al. (2018) [30]
Specimen Randomization	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	1	0	1	1	1	1
Single Operator	2	2	0	0	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2
Operator Blinded	2	2	2	0	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Standardized Specimens	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Control Group	2	2	2	2	0	2	2	0	0	2	0	0	0	2	0	2	0	0	0	2	2	0	2	0	2	2	2	0	2
Fractographic analysis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	2	0
Manufacturer's Instructions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sample Size Calculation	0	2	0	0	0	0	0	2	0	2	0	2	0	2	2	2	0	0	2	2	2	0	2	0	2	2	2	2	2
International Standards	1	0	1	1	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	0
Proper statistical analysis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	8	9	5	4	5	5	6	7	2	9	5	7	5	9	10	10	5	6	8	8	9	5	7	6	9	10	10	10	9
Risk of Bias	M	M	M	L	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Journal SJR score by date of publication	Q2	Q2	Q2	Q2	Q2	Q2	Q1	Q2	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q2	Q1	Q2	Q1	Q1	Q1	Q1	Q3	Q1	Q1	Q2	Q1	Q2	Q2

The description of specimen randomization and the control group were frequently inadequately described or lacking. The journal rankings are Q1 (62.07%), Q2 (34.48%), and Q3 (3.45%).

3.3. Descriptive Data

Data extraction recovered the information summarized in Tables 2 and 3. A synopsis of the CAD-CAM materials evaluated in the studies by type and physical properties is presented in Table 4. Lava Ultimate and Vita Enamic blocks were the most tested CAD-CAM blocks. Rely X Ultimate 2 was the most widely used resin cement, followed by Rely X Unicem, Rely X Ultimate, and Rely X U200, and μTBS was the most used test.

Table 2. Resumé of extracted data from selected studies assessing adhesive strength.

Author, Year	Material	Sample Pairing	Type of Test	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement
Abdou et al. (2021) [7]	Katana Avencia	Bovine incisors (n = 15)	µTBS	50 µm Al_2O_3 37.5% PA	Kerr Silane primer SB-UA Clearfil Universal Bond Quick	Clearfil Universal Bond Quick SB-UA Optibond all-in-one	Panavia V5 Rely X Ultimate NX3 Nexus
Albelasy et al. (2021) [31]	IPS. e max CAD Vita Enamic Lava Ultimate	Human molars (n = 14)	Ultimate fracture test; thermocycling failure pattern	50 µm Al_2O_3 8% HF 37% PA	Dentobond Silane	N/A	Rely X Unicem
Ali et al. (2012) [33]	Zirconia	Human molars (n = 12)	Load-to-fracture; thermocycling	50 µm Al_2O_3	N/A	ED primer	Panavia F 2.0 Rely X Unicem Clearfil SA
Augusti et al. (2020) [34]	Zirconia	Zirconia abutments (n = 10)	Pull-out test	50 µm Al_2O_3	N/A	N/A	Rely X Unicem 2
Bayazit et al. (2019) [8]	Lava Ultimate Vita Enamic	Blocks (n = 15)	µTBS	50 µm Al_2O_3 9.5% HF	N/A	SB-UA	Rely X U200 Set PP
Ceci et al. (2016) [9]	Lava Ultimate	Bovine incisors (n = 10)	µSBS	50 µm Al_2O_3 35% PA Clinpro powder (glycine)	SB-UA	SB-UA	Rely X Ultimate Rely X Unicem 2
Elsaka et al. (2014) [35]	Vita Enamic Lava Ultimate	Composite resin block (n = 3)	µTBS; aging	50 µm Al_2O_3 9.5% HF	Silane	N/A	Bifix SE
Ender et al. (2016) [3]	IPS. Empress CAD ArtBlock Temp	Human molars (n = 12)	SBS	50 µm Al_2O_3	Monobond Plus	Heliobond	Rely X Unicem Variolink II
Higashi et al. (2016) [1]	Katana Avencia	Luting cement (n = 8)	µTBS; aging	50 µm Al_2O_3	Clearfil Ceramic Primer Plus	N/A	Panavia V5 Panavia SA
Kawaguchi et al. (2016) [10]	Katana Avencia	Luting cement (n = 8)	µTBS; aging	50 µm Al_2O_3 40% PA K-Etchant gel	Clearfil Ceramic Primer Plus	N/A	Panavia V5 Panavia SA
Liebermann et al. (2013) [2]	ArtBlock temp	Luting cement (n = 20)	TBS; surface energy; surface roughness	50 µm Al_2O_3	N/A	Visiolink	Clearfil SA Rely X Unicem
Magne et al. (2015) [36]	Vita Mark II IPS. e max CAD Lava Ultimate	Human molars (n = 15)	Fatigue test	50 µm Al_2O_3 27 µm Al_2O_3 5% HF	Rely X Ceramic Primer	N/A	Rely X Unicem 2
Malysa et al. (2022) [37]	IPS Empress CAD IPS. e max CAD IPS. e max ZirCAD	Human Molars (n = 12)	SBS; load-to-fracture; thermocycling	9% HF 37% PA	N/A	N/A	Panavia V5 Maxcem Elite Rely X U200 Panavia SA

Table 2. *Cont.*

Author, Year	Material	Sample Pairing	Type of Test	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement
Nagasawa et al. (2021) [38]	Cerasmart Shofu Block HC HZR-CAD HR2 Estelite Vita Enamic Katana Avencia	Resin composite disk (n = 15)	SBS	70 µm Al_2O_3 15–40% PA 9% HF	GC G-Multiprimer	N/A	G-Cem ONE
Nagasawa et al. (2022) [14]	GN I Ceramic Block Cerasmart	Resin composite disk (n = 15)	SBS	70 µm Al_2O_3	GC G-Multiprimer GC Ceramic Primer II	N/A	G-Cem ONE
Nakamura et al. (2016) [39]	Zirconia	Luting cement (n = 10) Crown (n = 6)	Load-to-failure test; micro-CT analysis	N/A	ED primer	N/A	RelyX Unicem 2 Panavia F2.0
Oda et al. (2021) [25]	Katana Avencia	Human molars (n = 5)	µTBS; irradiance measurements	50 µm Al_2O_3 35% PA	Clearfil Ceramic Primer Plus	Clearfil SE Bond 2	Panavia SA Plus Panavia SA
Peumans et al. (2016) [40]	Celtra Duo IPS. e max CAD IPS Empress CAD Vita Enamic Vita Mark II Lava Ultimate	Block to block (n = 10)	µTBS	27 µm Al_2O_3 30 µm Al_2O_3 <5% HF 600-grit Sic Paper Cojet-SiO_2	Monobond Plus Heliobond	N/A	Clearfil Esthetic Panavia SA
Poggio et al. (2016) [6]	Lava Ultimate	Bovine incisors (n = 10)	SBS	35% PA	SB-UA	SB-UA	Rely X Ultimate Rely X Unicem 2
Preis et al. (2015) [4]	Celtra Duo IPS. e max CAD	Human molars (n = 8)	Thermal cycling and mechanical loading (chewing machine)	5% HF	Monobond S	Heliobond	Smart Cem 2 Variolink II
Sorrentino et al. (2016) [41]	Zirconia	Human molars (n = 10)	Load-to-fracture	50 µm Al_2O_3	N/A	N/A	G-Cem LinkAce
Takahashi et al. (2022) [42]	Estelite P Katana Avencia Shofu Black HC Super Hard	Luting cement (n = 10)	SBS	50 µm Al_2O_3	N/A	HC Primer	Panavia SA Block HC Cem
Ustun et al. (2021) [27]	Vita Suprinity Vita Enamic Cerasmart	Human molars (n = 7)	SBS; thermocycling	5% HF 37% PA	Ultradent Porcelain Silane	SB-UA	Rely X Ultimate Rely X U200
Zahoui et al. (2020) [43]	Zirconia	Ti-base CAD/CAM abutments (n = 10)	Pull-out test	30 µm Al_2O_3 45 µm Al_2O_3	SB-UA	SB-UA	Rely X U200 Rely X Ultimate
Zhang et al. (2018) [51]	Zirconia	Luting cement (n = 20)	µSBS	50 µm Al_2O_3	SB-UA	SB-UA	Multilink Speed

Al_2O_3, aluminum oxide; HF, hydrofluoric acid; PA, phosphoric acid; N/A, not applied; SB-UA, Scotchbond Universal Adhesive; SiC, silica paper abrasive.

Table 3. Resumé of extracted data from selected studies assessing the marginal gap.

Author, Year	Material	Sample Pairing	Type of Test	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement
Dauti et al. (2020) [5]	Vita Enamic	Model resin (n = 10)	Micro CT scan Marginal adaptation measurements	5% HF	Monobond Plus	AdheSE primer AdheSE Adhesive Optibond XTR OptiBond XTR Primer OptiBond XTR Bond	Rely X Unicem Variolink Esthetic NX3 Nexus
Ender et al. (2016) [3]	IPS. Empress CAD ArtBlock Temp	Human molars (n = 12)	Marginal adaptation, chewing fatigue test	50 µm Al_2O_3	Monobond Plus	Heliobond	Rely X Unicem Variolink II
Han et al. (2020) [28]	Lava Ultimate	Human molars (n = 6)	Thermocycling; interfacial adaptation	50 µm Al_2O_3 Polyacrylic acid	N/A	Universal dentine adhesive Clearfil Universal bond quick Ceramic Primer Plus	Panavia V5 Rely X U200 G-Cem LinkAce SmartCem2 Multilink speed
Kirsten et al. (2018) [26]	Vita Mark II	Human molars (n = 8)	Evaluation of crown integrity and cement gap thickness	35 µm Al_2O_3 37% PA 5% HF	N/A	Syntac	iCEM Rely X Unicem 2 Variolink Esthetic
Melo Freire et al. (2017) [22]	IPS. e max CAD IPS. e max Press	Bovine teeth (n = 64)	Marginal adaptation SEM	10% HF 35% PA	Rely X Ceramic Primer	Adper Single Bond Plus	Rely X ARC Rely X U200
Preis et al. (2015) [4]	Celtra Duo IPS. e max CAD	Human molars (n = 8)	Thermocycling; marginal quality (i) intact margin (ii) marginal gap	5% HF	Monobond S	Heliobond	Smart Cem 2 Variolink II

Al_2O_3, aluminum oxide; HF, hydrofluoric acid; PA, phosphoric acid; N/A, not applied.

Table 4. Synopsis of the CAD-CAM ceramic blocks by type of material based on the manufacturer's official datasheet.

Material	Type of Material	Physical Properties	Manufacturer
ArtBlock Temp	Bis-acrylic composite blocks for temporary crowns and bridges. Highly cross-linked interpenetrated PMMA, the OMP-N (organic modified polymer network), without inorganic fillers	Flexural strength: > 90 MPa Module of elasticity: 2.680 MPa Organic curing agent OMP-N Does not contain inorganic fillers	Merz Dental GmbH, Germany
Celtra Duo	Zirconia-reinforced lithium silicate ceramic	Median load fracture: 725 N Fracture toughness: 2.6 MPa·$m^{1/2}$	Dentsply Sirona, Germany
Cerasmart	Hybrid ceramic composite	Flexural strength: 238 MPa Breaking energy: 2.2 N/cm Preserved marginal integrity	GC Corporation, Japan
Estelite	Submicron-filled composite	Flexural strength: 259 MPa Elastic modulus: 13.8 GPa	Tokuyama Dental Corporation, Japan
GN I Ceramic Block	Hybrid ceramic composite material with inorganic fillers (silica, zirconia, and alumina)	Flexural strength: > 500 MPa Low thermal conductivity Color stability	GC Corporation, Japan
HZR-CAD HR2	Hybrid ceramic with ceramic cluster filler (1–20 µm)	Flexural strength: > 250 MPa Sustained fluoride release High abrasion resistance	Yamakin, Japan
IPS Empress CAD	Lithium disilicate glass-ceramic	Biaxial flexural strength: 185 MPa	Ivoclar Vivadent, Liechtenstein
IPS. e max CAD		Biaxial flexural strength: 530 MPa Fracture toughness: 2.11 MPa·$m^{1/2}$ Rapid crystallization: 11 min	
IPS. e max Press		Flexural strength: 470 MPa Fracture toughness: 2.5–3 MPa·$m^{1/2}$	
IPS. e max ZirCAD	Zirconium oxide	Flexural strength: 850–1200 MPa	
Katana Avencia	Hybrid ceramic (nanosized fillers densely compressed into block and infused with resin monomer)	Flexural strength: > 220 MPa Compressive strength: > 600 MPa Excellent wear resistance	Kuraray Noritake, Japan
Lava Ultimate	Highly cross-linked polymeric matrix embedded with 80% of nanoceramic components	Elastic modulus similar to dentin High resistance to fracture	3M ESPE, USA
Shofu Block HC	Pre-sintered, highly filled hybrid ceramic block made of zirconia-reinforced lithium silicate	Stress-absorbing hybrid-ceramic material Flexural strength: > 190 MPa Excellent handling and milling properties	SHOFU Dental GmbH, Japan
Vita Enamic	Hybrid ceramic with a dual ceramic-polymer network structure	Flexural strength: ± 160 MPa Module of elasticity: 3 MPa Fracture toughness: 1.5 MPa·$m^{1/2}$	Vita Zahnfabrik, Germany
Vita Mark II	Fine-structure (4 µm) feldspar ceramic	Flexural strength: 150-160 MPa Elastic modulus: 30.0 GPa Static fracture load: 2.766 N	
Vita Suprinity	High-strength zirconia-reinforced lithium silicate ceramic material	Flexural strength: ± 420 MPa Module of elasticity: 7 MPa Fracture toughness: ± 2.0 MPa·$m^{1/2}$	
Zenostar	Zirconium oxide	Flexural strength > 900 MPa Good abrasive characteristics Gingiva-friendly	Wieland, Germany

3.4. Meta-Analysis

For quantitative analysis, 12 studies were sub-grouped to evaluate mechanical performance [1,2,6–10,25,27,35,37,42] and four [3–5,26] to evaluate marginal parameters. Five articles initially thought to be included were rejected for the meta-analysis because they provided no quantitative results, making inclusion impossible for mechanical [14,38,40] or marginal assessment [22,28]. Table 5 lists the blocks found in the studies that evaluated the mechanical performance and the relative number of tests available.

Table 5. CAD-CAM blocks identified in articles for quantitative analysis.

Material	Frequency	Percent	Cumulative
Artblock Temp	12	4.48	4.58
Cerasmart	28	10.69	15.27
Estelite block	13	4.96	20.23
HZR-CAD-HR2	5	1.91	22.14
IPS Empress CAD	12	4.58	26.72
IPS e. max Zircad	12	4.58	31.30
IPS e. max CAD	12	4.58	35.88
Katana Avencia	97	37.02	72.90
Lava Ultimate	25	9.54	82.44
Shofu Block Hc	13	4.96	87.40
Vita Enamic	27	10.31	97.71
Vita Suprinity	6	2.29	100.00
Total	262	100.00	

The meta-analysis combining the selected 12 articles based on the difference between means and the effect size (p = 0.05; 95% CI; Z-value 1.9599) for mechanical performance is shown in Figure 2.

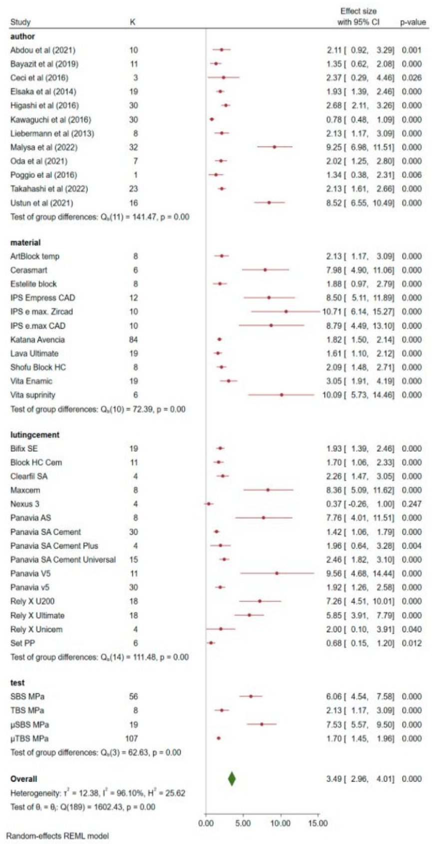

Figure 2. Forest plot summarizing the effect size of the author, CAD-CAM block, luting cement, and mechanical tests with data obtained from the included studies [1,2,6–10,25,27,35,37,42].

The assessment of publication bias and heterogeneity for these subgroups of articles is shown in Figures 3 and 4, respectively. Heterogeneity is expected when assessing studies with different tests and substrates. Even so, it is essential to analyze this heterogeneity, as it is entirely different to find a total dispersion of studies or to find a tendency towards aggregation, as is the case. Funnel plot asymmetry suggests an overestimation of the intervention effect, probably induced by the disparity between samples, with some possible bias. The Galbraith plot suggests some heterogeneity among the effect sizes, as although most of the studies were within the 95% CI region, several were outside. All studies had high precision (toward the right of the X-axis). Globally, the studies were above the green line, with the red line sloping upward, suggesting favorable testing protocols compared to the control protocol. The biplot graph in Figure 5 displays the means and standard deviations (SD) of some tested material–luting cement pairs and reveals heterogeneous mechanical performance among the tested protocols. The graph suggests a similar behavior for most pairs of adhered substrates but also some performance disparities.

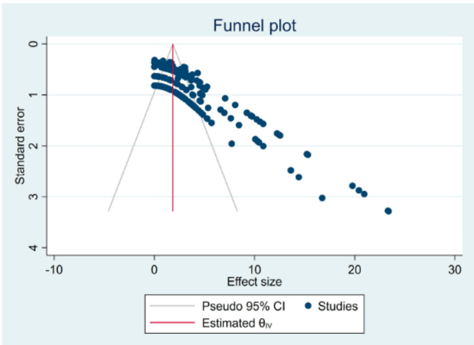

Figure 3. Funnel plot of publication bias of all selected publications, filtered by the joint substrate and mechanical tests.

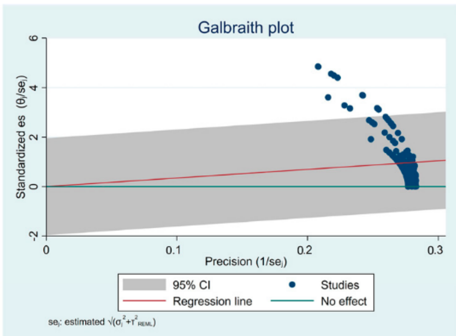

Figure 4. Heterogeneity assessment of effect sizes.

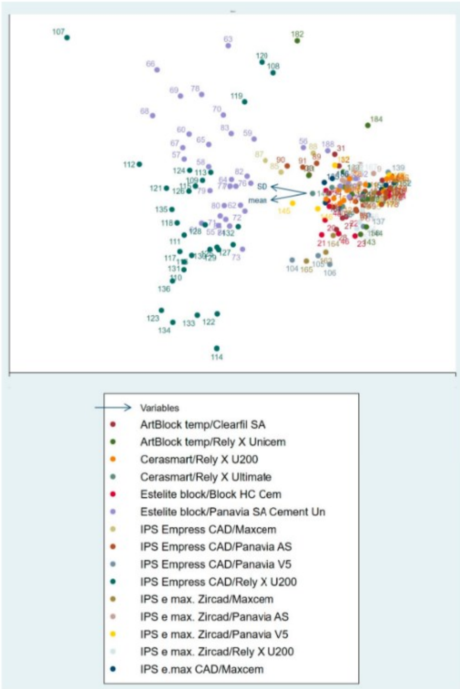

Figure 5. Biplot graphs of mean and standard deviation (SD).

Figure 6 shows that the Variolink II cement provides resistance to Celtra DUO blocks and IPS emax CAD. The latter is also resistant when cemented with Rely X Unicem, a cement proven to exhibit excellent and universal performance.

Figure 6. Radar graphs with load-to-fracture by CAD-CAM block and luting cement. [1,2,6–10,25,27,35,37,42].

Figure 7 shows that the Vita Enamic block has an irregular behavior for the marginal parameters evaluated, regardless of the cement used. Concerning the marginal gap, the Vita Mark II (feldspathic ceramic) has an excellent marginal fit.

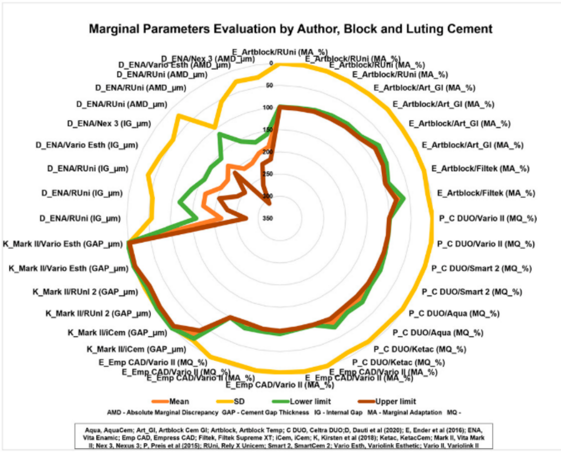

Figure 7. Radar graphs with marginal parameter evaluation by author, CAD-CAM block, and luting cement [3–5,26].

4. Discussion

This review assessed whether self-adhesive resin-matrix composite cement (SARC) is adequate for the luting cementation of CAD-CAM ceramic blocks and which is the best luting cement adhesive protocol for each block. Based on the existing data ($p < 0.05$), it was accepted that self-adhesive resin-matrix cement systems are effective in cementing CAD-CAM blocks on different substrates and rejected the hypothesis that self-adhesive resin-matrix cement performs better than conventional resin-matrix cement. Moreover, it was not possible to establish a luting cement that suits a particular CAD-CAM block, or if there is a better SARC adequate for all situations, which agrees with a recent publication for luting protocols [11].

Before a detailed discussion of the results of the available studies, general considerations must be made. When evaluating laboratory studies, one must always consider that their ultimate purpose should be to find solutions that can be implemented in a clinical environment to improve the quality of restorative options. In addition, the adhesive cementation of a CAD-CAM ceramic restoration to dental structures depends on a complex adhesive joint. This joint is formed by two interfaces: one between the dental structures (enamel and/or dentin) and the luting cement, and the other between the luting cement and the CAD-CAM ceramic. This last aspect has led to research focusing on adhered restorations as a whole, on the cement–tooth interface, or on the cement–restoration interface. It should also be mentioned that using bovine teeth for laboratory tests is a common practice that overcomes some ethical constraints of using human teeth. These teeth are considered credible substitutes, with a mechanical and adhesive behavior similar to human teeth [52,53]. Finally, to overcome the fact that the substrates used in the studies, as well as the protocols tested, were frequently different, the adhesive strength was compared only between blocks studied in at least two studies and within the same study each adhesive protocol was compared used with different CAD-CAM blocks.

Several studies have been conducted on SARCs. SARCs exhibited different adhesive strengths depending on which CAD-CAM block was evaluated, how the surface was treated, and which luting cement was used. Thus, many criteria must be considered for the luting success of the CAD-CAM blocks.

Adhesive cementation with SARC is less technique-sensitive and time-consuming than conventional methods because it bonds to an unconditioned tooth surface without the need for pretreatment with an acid or adhesive, allowing placement of the restoration in a single step. However, several strategies to treat the substrate surface before applying self-adhesive resin cement have been developed to improve bond strength.

4.1. Surface Treatment

The most frequently used treatment in the selected studies was sandblasting with 50 µm aluminum oxide particles (Al_2O_3). For resin-matrix ceramic, surface treatment is the most critical factor affecting the bond strength between the resin cement and the CAD-CAM material, followed by the type of resin-matrix ceramic and the resin cement, respectively [8]. Sandblasting has been proposed as the preferred pretreatment for CAD-CAM hybrid ceramics with high ceramic content, such as Vita Enamic [8]. In contrast, pre-treatment with hydrofluoric acid (HF) is recommended for CAD-CAM resin nanoceramics reinforced with nanoparticles, such as Lava Ultimate. Nevertheless, it was found that in hybrid ceramics, such as Vita Enamic, surface treatment with HF and a silane coupling agent showed higher bond strength values than sandblasting or HF alone. Vita Enamic coupled with Bifix (SARC) appears more hydrolytically stable and durable than Lava Ultimate coupled with the same SARC [1,35]. Recently, it was advocated that sandblasting or HF followed by a universal adhesive could also be used with effectiveness as pre-treatment [15].

Other studies [14,38] found that the priming or sandblasting of the CAD-CAM composite and ceramic blocks significantly increased the bond strength of SARCs compared to non-treated controls. In addition, bond strengths obtained by 9% HF etching and priming were comparable to those obtained by sandblasting and priming [38]. Other surface treatments were investigated in different studies, such as polyacrylic acid, with no significant difference in the interfacial adaptation of resin nanoceramic inlays [28]. Additionally, surface treatment with plasma of an organic modified polymer infiltrated network (PMMA) block did not increase the adhesion to SARC despite increased surface energy, with no impact on surface roughness and a negative impact on the bonding with dental resin-matrix materials [2]. Furthermore, pre-treatment with glycine did not significantly change the bond strength in the various luting protocols tested. Still, it increased the bond strength of self-adhesive resin cement, so it needs further investigation [9]. Studies concerning ultrasonic and acid cleaning after sandblasting suggest that as long as the restorations are sandblasted after the try-in procedure in a clinical setting, there is no need for ultrasonic and acid cleaning after sandblasting to improve the microtensile bond strength [10].

Disparities were described in the optimal surface treatment and resin cement selection for Vita Enamic and Lava Ultimate resin-matrix ceramic blocks [40]. For Lava Ultimate (resinous matrix composite densely packed with silica and zirconia particles), sandblasting pretreatment was proposed, but hydrofluoric acid etching significantly positively affected bond strength. In terms of resin cement, the self-adhesive material (Panavia SA Cement) outperformed the conventional resin cement (Clearfil Esthetic Cement) in terms of bond strength to Lava Ultimate [40]. Today, Lava Ultimate is still indicated for inlays, onlays, and veneers, but the manufacturer has removed the crown indication since June 2015 because of the higher rates of premature debonding. Recently, a meta-analysis [11] revealed as a better protocol for Lava Ultimate, sandblasting with 50 µm Al_2O_3 and an SARC (G-Cem LinkForce) + Universal Primer (G-Multi Primer), and as the worst protocol, the use of no sandblasting and an SARC (RelyX Unicem 2) used alone. In contrast, the surface treatment had little effect on the bonding to Vita Enamic (a ceramic structure infiltrated with resin). The manufacturer recommends silane as the best surface treatment, alone or after HF. However, the self-adhesive resin cement demonstrated a lower overall bond strength within the same surface treatment group than conventional resin cement [35]. This variance in results can be explained by using different methodologies and materials and the lack of a separate adhesive layer in self-adhesive resin cement. Even though some results are contradictory, most studies recommend HF and silane as surface treatments for Vita Enamic or a universal primer [11,15].

Concerning the fabrication of monolithic zirconia crowns with reduced crown thickness to a lower limit of 0.5 mm, it was described that regardless of the cement type, the crown still had sufficient strength to withstand occlusal loads, with less invasiveness of the preparation and tooth tissue preservation [39,41]. Furthermore, adequate retention and resistance designs heightened the zirconia coping retention compared to copings cemented on teeth lacking these forms. Interestingly, upon failure, the cement mainly remained on the tooth if an adhesive resin cement was coupled with a bonding system. In contrast, the cement remained mainly on the coping with self-adhesive resin cement [33], reflecting adhesive failure. When comparing the bonding strength between a felspathic ceramic, a disilicate ceramic, and a zirconia ceramic bonded with three different SARCs and a conventional multi-step resin cement, the zirconia ceramic had the lowest bond strength among the tested ceramics, regardless of the tested cement [37], highlighting the possibility of using another strategy for this material whenever esthetic issues are absent [15,50].

4.2. Interaction between Substrates

Since SARC reacts superficially with mineralized tissues, this self-adhesive resin cement does not form a strong dentin hybrid layer or resin tags [25]. Resin coating with a hydrophobic resin may be suggested, as it creates a layer with a low modulus of elasticity that acts as a stress breaker or shock absorber, resulting in higher bond strengths with the resin-coated groups, strengthening the dentin interface, thus leading to better adhesive performance, regardless of the resin cement and its curing mode [7,25,50].

The dual-curing mode exhibited a higher bond strength than the self-curing mode. The slow-curing process in the self-curing mode allows water to be absorbed from the dentinal tubules by osmosis. Therefore, a resin coating plays a role in suppressing water penetration through the adhesive layer, especially in the self-curing mode [23,25,50]. Furthermore, single-visit treatment results in a higher bond strength between resin cement, dentin, and CAD-CAM blocks than multiple-visit treatments, even with resin coating [7,23].

In general, self-adhesive resin cement is inherently a self-etching material during the initial stages of its chemical reaction. After mixing, its low pH and early high hydrophilicity result in good tooth structure wetting and promote surface demineralization, similar to self-etching adhesives [23,50]. As the reaction progresses, cement acidity is gradually neutralized by the reaction with the tooth substrate apatite and the metal oxides contained in the basic and acid-soluble inorganic fillers. Cement becomes more hydrophobic as chemical reactions in situ consume hydrophilic and acidic monomers. This is highly desirable in a fully cured resin to minimize water sorption, hygroscopic expansion, and hydrolytic degradation [26].

Self-adhesive resin cement with a lower pH-neutralizing capacity has higher residual hydrophilicity and higher hygroscopic expansion [45]. Water sorption and significant hygroscopic expansion stresses can result from the residual hydrophilicity during and after the setting reaction. Whenever a self-adhesive resin cement is a clinical option, cement with a strong neutralization reaction is recommended, resulting in lower hygroscopic expansion strain [45]. Cracks can be attributed to the hygroscopic expansion stress of the build-up and luting material, and it is possible that the storage of specimens in distilled water increases the rate of water uptake, resulting in higher hygroscopic expansion stresses [26].

Incorporating acidic monomers with hydrogen bonding sites, such as hydroxyl, phosphate, or carboxyl groups, contributes to the natural hydrophilicity of SARCs compared with conventional resin cement. SARCs with poor pH neutralization and high hygroscopic expansion stress can cause fractures in feldspathic ceramic crowns. This phenomenon can be increased by pre-damaging during CAD-CAM processing [26]. For this, in clinical use, in conjunction with CAD-CAM crowns, SARCs with increased pH neutralization behavior and low hygroscopic expansion stress are preferred [15,22].

4.3. Adhesive Strategy

Luting strategies fall into adhesive or non-adhesive strategies, but adhesive luting reinforces the mechanical properties of the CAD-CAM ceramic used as a restorative material, excepting zirconia polycrystals [20]. An adhesive luting strategy could be conventional multi-step or self-adhesive [50]. Self-adhesive resin cement aimed to reduce these conventional steps [8]. Conventional multi-step resin luting (with etch-and-rinse, self-etch adhesives, or priming) enables higher adhesive strength values of the bonding interfaces than the self-adhesive strategy alone [1,11,42,45], especially when a conventional resin cement is combined with a self-etch adhesive [6].

The clinical use of SARC results in less postoperative sensitivity than resin-modified glass ionomer cement and glass ionomer cement. However, the adhesive strength values of self-adhesive resin cement bonded to both enamel and dentine are lower than those of conventional multi-step resin cement [50].

This study found self-adhesive resin cement is not recommended for restorations with reduced retention and resistance, such as resin-bonded bridges and crowns with low heights. This is in line with the literature [50]. Similarly, veneers require a strong bond to the tooth structure to ensure their longevity and prevent discoloration; self-adhesive resin cement may not provide the necessary bond strength, especially in cases with weak enamel bonding [50]. In such cases, conventional or dual-cure resin cement may be more appropriate [45,50].

Assessment of the fatigue resistance of ultrathin CAD-CAM crowns cemented with SARC (Rely X Unicem 2) revealed the possibility of using resin nanoceramics and lithium disilicate to restore posterior teeth with regular or ultrathin crowns, even with relatively high loading requirements. However, SARCs should not be used for ultrathin crowns with feldspathic ceramic veneers. The immediate dentin sealing (IDS) technique should be used with preheated composite resin as a luting agent [36]. Poly(methyl methacrylate) (PMMA)-based CAD-CAM inlays, luted with self-adhesive resin cement, may be applied as long-term restorations in narrow cavities based on the findings of marginal adaption, fracture load, and fracture analysis [3].

Considering the material strength and chemical characteristics of Vita Suprinity ceramic restorations, both total-etch and self-adhesive systems may be recommended. However, the self-adhesive systems with a lower pH neutralizing capacity allow more hydrolysis and chemical degradation over time than a total-etch system [27,45]. Furthermore, self-adhesive rather than total-etch systems are appropriate for performing Vita Suprinity ceramic restorations in deep cavities with high postoperative sensitivity. It is possible to recommend cementing Vita Enamic and GC ceramic restorations with self-etch systems. Regardless of the cementation system, the thermal aging process significantly reduced the bond strength values of all ceramic materials [27].

Only three clinical studies were found during the manual search [24,47,48]. A prospective randomized clinical trial (RCT) testing the selective etching of enamel in the cementation of partial ceramic crowns with SARCs [24] with control at 12, 24, and 36 months found the potential to improve restoration survival rates in challenging clinical situations. Another RCT with control at 6, 12, and 18 months found no statistically significant difference in the survival rates, surface texture, secondary caries, anatomic form, color match, marginal discoloration, marginal integrity, interproximal contacts, and patient satisfaction between CAD/CAM-fabricated resin nanoceramic inlay/onlay restorations cemented with either a self-adhesive after selective enamel etching or a universal adhesive/resin cement system [47]. In contrast, an RCT using a split-mouth model, with evaluation after 39 months, found significant differences in luting adhesive strategies and stated that self-adhesive resin cements could not be recommended for luting partial ceramic, but instead, a luting procedure with a luting composite coupled with a universal adhesive yielded promising clinical results with or without the use of a selective enamel etching step [48].

Currently, SARCs are not recommended for luting partial ceramic crowns.

Regarding the most effective cementation protocol for bonding zirconia crowns to Ti-base CAD-CAM abutments in terms of abutment height, cement type, and surface treatment, it was found that conventional resin cement associated with self-etch adhesive displayed higher retention than self-adhesive cement and that high abutments presented higher retention pressures than short ones. Hierarchically, the results showed a direct correlation between Ti-base height, micro-mechanical and/or chemical pre-treatment, Ti-base surface blasting, and zirconia, and that tribochemical and silica coating increased the retention of zirconia crowns, followed by Ti-base surface blasting or tribochemical silica coating [43].

4.4. Coupling Agents

The association of a universal adhesive or primer with self-adhesive resin cement to attach to CAD-CAM composite blocks significantly increased the bond strength compared with the self-adhesive resin cement used alone for the same period. Still, surface treatment is a more important factor affecting the bond strength of resin cement to the resin-matrix ceramic than the specific cement used [8,38]. Recently, it was suggested that silane could be successfully adjoined to the hydrophobic paste of a self-adhesive composite cement, eliminating the need for a separate silanization step, thus simplifying the adhesive bonding process [44]. SARCs must be presented as two-part materials, usually in separate individual syringes or more popular dual-barrel syringe dispensers [45], with the last presentation being unfavorable for silane addition.

However, a study that evaluated the bond strength between nanoceramic materials and bovine dentin using various adhesive systems reported that conventional multistep resin cement (coupled with etch-and-rinse or self-etch adhesives) showed better shear strength values than SARCs. Moreover, association with self-etch adhesive resulted in the highest values of adhesion bonds, and adding silane to the surfaces of the resin matrix ceramics increased the shear bond strength [6].

The one-step self-etch adhesive differs from two-step self-etch adhesive. An extra hydrophobic bonding resin applied over the acidic primer for the two-step self-etch adhesives turns it into the gold standard for the self-etch strategy [23]. Nevertheless, most universal adhesives must be mixed with the respective dual-cure activator when used with self- or dual-cure composite materials, such as build-up materials and resin cement with aromatic tertiary amines in the initiator system [23].

When adhering to the tooth structure, selective enamel etching with phosphoric acid (PA) is recommended without etching the dentin, allowing potential chemical bonding between the functional monomer and dentin hydroxyapatite. Universal adhesives may also need extra solvent drying time to ensure the removal of the residual water in the interface [23].

Systematic reviews evaluating adhesion to zirconia have shown that using MDP-based self-adhesive cement yields more favorable results after physicochemical conditioning of the zirconia surface. Although water storage may affect the bond strength of resin cement to zirconia, no difference was found between the cements for a specific aged dataset. This may confirm that cement choice is less critical for zirconia-bond durability [45].

4.5. Dimensions of the Interface and Marginal Adaptation

Milled ceramic restorations cemented with self-adhesive resin cement result in a thinner cement line with the highest interface quality correlated with a thin cement interface [22]. Concerning hybrid ceramics (polymer-infiltrated ceramic network) crowns, the marginal and internal fits were not significantly affected by the different virtual spacer settings of 50 µm and 80 µm, and for those settings and three different resin luting materials (Rely X Unicem, Variolink Esthetic DC, Nexus 3) no significant influence was discovered in the marginal and internal fit [5]. In all investigations, porosities in the cement space on the periphery in contact with the outside environment were found. In the clinical setting, unprotected dentin can be contaminated through these voids by fluids, bacteria, and bacterial toxins, which could compromise the efficacy of the restoration [5]; a fact associated with plaque accumulation and a higher bleeding score around prostheses cemented with the resin cement [45] advises the removal of excess material at the restoration margins after brief light-activation (2–3 s from each side) in the case of light- or dual-cured cement [26].

As for the excess cement at the marginal adaptation, despite the cleaning process, similar quantities of undetected cement remnants were found around the esthetic margins of zirconia crown copings, regardless of the type of cement (conventional glass-ionomer or SARC). Cleaning procedures with clinically accessible instruments did not allow the complete removal of excess cement [34].

4.6. Toxicity and Aging

The in vitro cytotoxicity of an SARC used to cement a zirconia crown seems to be influenced by the inclination of the crown cusps, regardless of the curing time (20 s or 40 s). However, the cytotoxicity of a zirconia crown with a thickness of 1.0 mm conforms to ISO standards when the cusp inclination is less than 20 degrees but does not meet those standards when the cusp inclination of zirconia reached or exceeded 30 degrees [30]. In addition, the in vitro cytotoxicity of SARCs can be reduced by extending the light-curing period, which aligns with the literature for other restorative resin composites [29]. SARCs have different cytotoxic and apoptotic effects that increase with increased exposure time to non-converted monomers [46], drawing attention to the need for efficient polymerization and excess removal.

Among the studies found, the parameter of aging is not always considered or is not standardized, in line with the literature [11,20]. Generally, thermal aging reduces the bond strength values of all the interfaces studied, regardless of the cementation procedure. Still, resin cements are less prone to degradation in water than conventional acid-base cements and can maintain their properties for extended periods [1,11,20,27,37]. Clinicians should consider these variables and choose the most suitable cementation systems for each material [11,27].

Thermocycling affected the shear bond strength of self-adhesive, self-etching resin cements luted to human dentin and CAD-CAM ceramics, revealing that conventional resin cement (Panavia V5) demonstrated a significantly higher bonding strength than self-adhesive and self-etching cements, with significant differences in the bond strengths for the studied combinations. The most significant decreases in bond strength were observed for self-etching, self-adhesive cements when comparing samples that had not been thermocycled to those that had been artificially aged [37].

In addition, aging and deterioration often occur without visible catastrophic failures, particularly with high-strength ceramics [4]. Zirconia-reinforced lithium silicate ceramics exhibit high flexural strength and, at the same time, high translucency. Strong fracture forces, high resistance to aging, and good-to-adequate marginal adaptability have been observed, [4] indicating that no limitations should be anticipated for clinical use.

Glass ionomer cement, resin, and resin-modified self-adhesive luting materials are suitable for the cementation of molar crowns made of zirconia-reinforced lithium silicate ceramics.

5. Conclusions

SARCs perform well in mechanical tests but differ and do not necessarily produce similar results. Surface treatment of CAD-CAM ceramic restorations is mandatory before cementation, regardless of the SARC type. The effect of the surface treatment is material-dependent. For all types of ceramics, surface treatment or cement light-curing improved the adhesion compared with the SARC used alone and in the self-cured mode. Sandblasting is preferred for hybrid ceramics, while hydrofluoric acid is recommended for resin nanoceramics reinforced with nanoparticles and glass ceramics. A cement line with a reduced thickness correlates with a better interface quality. SARCs with increased pH neutralization behavior and low hygroscopic expansion stress are preferred for clinical use, and an extended light-curing time reduces the in vitro cytotoxicity of SARCs. Immediate dentin sealing improves the bond strength between dentin and CAD-CAM ceramic bocks. Single-visit treatments yield a higher bond strength than multiple-visit treatments. CAD-CAM zirconia crowns with an occlusal thickness of 0.5 mm, cemented with an SARC, withstand occlusal loads. Glass ionomer cements, resin, resin-modified glass ionomer cement, and self-adhesive luting materials are suitable for the cementation of molar zirconia-reinforced lithium silicate crowns, and the cement is less critical for bond durability than proper tooth preparation, cleaning, and drying before cementation. Dual-cured self-adhesive resin cements provide significantly higher early retention values than resin-modified glass ionomer materials. Each CAD-CAM material/luting composite must be individually studied and evaluated to determine the optimal bonding protocol. There is an urgent need for randomized clinical trials or at least an extensive, well-documented series of clinical cases.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ma16082996/s1, Table S1: Effect size calculation.

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A Polymer-Infiltrated Ceramic as Base Adherent in an Experimental Specimen Model to Test the Shear Bond Strength of CAD-CAM Monolithic Ceramics Used in Resin-Bonded Dental Bridges

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Abstract: Traditional load-to-failure tests fail to recreate clinical failures of all-ceramic restorations. Experimental fabrication, similar to prosthetic laboratory and clinical procedures, best predicts future clinical performance. A hybrid ceramic adherend, mechanically similar to a human tooth, was tested by comparing the shear bond strength (SBS) and fracture mode of four restorative materials adhered with a dual-cure adhesive cement. Surface energy, shear bond strength (SBS), and fracture mode were assessed. Vita Enamic (ENA), Vita Suprinity (SUP), Vita Y-TPZ (Y-ZT), and a nanohybrid composite (RES) (control group) cylinders, adhered with RelyX Ultimate to ENA blocks were assembled in experimental specimens simulating a 3-unit resin-bonded dental bridge. The ENA adherend was ground or treated with 5% hydrofluoric acid for 60 s. Monobond Plus was used as the coupling agent. Mean shear stress (MPa) was calculated for each group. Forest plots by material elaborated after calculating the difference in means and effect size ($\alpha = 0.05$; 95% CI; Z-value = 1.96) revealed significant differences in the shear force behavior between materials ($p < 0.01$). RES (69.10 ± 24.58 MPa) > ENA (18.38 ± 8.51 MPa) > SUP (11.44 ± 4.04 MPa) > Y-ZT (18.48 ± 12.12 MPa). Y-ZT and SUP exhibited pre-test failures. SBS was not related to surface energy. The failure mode in the Y-ZT group was material-dependent and exclusively adhesive. ENA is a potential adherend for dental materials SBS tests. In this experimental design, it withstood 103 MPa of adhesive stress before cohesive failure.

Keywords: adhesive stress; bonding; hybrid ceramic; CAD-CAM; resin cement; resin-bonded bridge; shear bond strength; surface energy; surface treatment; zirconia-reinforced lithium disilicate; yttria-stabilized tetragonal zirconia

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1. Introduction

Computer-aided design-computer-aided manufacturing (CAD-CAM) materials are versatile and emerging as the materials of choice for many restorations. However, proper clinical and research-based evidence is required to confirm their success and durability before they can be recommended for patient care [1–3]. Scientific evidence is mainly based on laboratory tests. It has long been suggested [4] that traditional fracture tests of single-unit all-ceramic prostheses are inappropriate because they do not mimic the failure mechanisms observed in retrieved failed clinical specimens. Current evidence suggests as best predictors of future clinical performance are tests with full anatomy restoration design, interproximal wall-length variations, core shape and veneer thickness similar to clinical design, fabrication procedures following laboratory and clinical procedures, comparison of support structures present in the clinical context (e.g., implant- vs. dentin-supported), and fatigue load assessment in water with sliding contacts [5]. In addition, in vitro studies frequently do not simulate bruxism scenarios that often occur in vivo [6].

The high innovation rate of CAD-CAM materials and technology requires good knowledge for optimal and successful clinical use [7]. In a clinical, laboratory, or centralized environment, workflow options are endless, and the variety of technologies is vast, with increased levels of communication, predictability, productivity, efficiency, and patient care [8]. While subtractive techniques are primarily used for definitive restorative purposes, additive techniques, mainly used for treatment planning or temporary devices, offer potential material savings and are beneficial when creating complex geometries, with the disadvantages of high cost, time-consuming post-processing, low flexural strength, and lack of long-term clinical research essential to facilitate the translation of its applications from laboratory to clinical setting [9–11]. CAD-CAM monolithic ceramics aim to avoid the technical and mechanical issues associated with layered fixed prostheses and apparently have high survival and low complication rates [12,13]. Further randomized controlled trials (RCTs) are needed to evaluate their long-term clinical performance compared to veneered restorations [12]. Experimental in vitro research designs that simulate clinical conditions using a polymer-infiltrated ceramic as a standardized adherent to replace natural teeth can help to understand the behavior of materials and prostheses. To date, few experimental protocols have been transposed directly from laboratory studies to clinical contexts [1]. Laboratory tests performed on natural teeth have inherent biological variability, with implied heterogeneity of results, and confront ethical restrictions. Testing adhesive protocols brought from the clinic to the laboratory and not vice versa can contribute to clarifying the effectiveness of adhesive procedures in the clinical context as a part of rehabilitative treatment. Adhesive restorations rely on bonding systems to form micromechanical bonds with the teeth [14,15]. However, chemical interactions may occur between functional monomers and components, with potential benefits [16–18].

Resin-based cement is widely used to adhere to nonmetallic restorations. Bond strength tests are essential to study mechanical performance [16], as mechanical, thermal, and passive hydrolysis may occur in the mouth, resulting in loss of adhesive joint performance [19]. CAD-CAM esthetic materials fall into four main classes: glass-matrix ceramics, polycrystalline ceramics, indirect composites, and hybrid ceramics [20,21].

The CAD-CAM hybrid ceramic Vita Enamic (ENA) (VITA Zahnfabrik, Bad Säckingen, Germany) is based on a dominant ceramic network reinforced with an acrylic polymer network resin [20]. It combines a low flexural modulus with high flexural strength (150–160 MPa), which is expected to increase its ability to withstand loads by undergoing more elastic deformation before failure, similar to the behavior of human teeth [22]. The typical double-network microstructure of the ENA is essential for the micromechanical bonding and performance of the adhesive interface [23] owing to the decrease in crack propagation [24].

Vita Suprinity (SUP) (VITA Zahnfabrik, Bad Säckingen, Germany) is a versatile pre-crystallized zirconia-reinforced lithium silicate ceramic with easy milling and polishing. It has a fine-grained (0.5–0.7 μm) and homogeneous structure, with a consistently high load capacity (flexural strength, crystallized at 420 MPa) [25]. Despite the biocompatibility and mechanical properties of SUP, data are still scarce, often controversial, and limited to short-term observational periods, which require further in vitro/in vivo studies primarily for long-term performance [26]. The polycrystalline ceramic Vita YZ HT (Y-ZT) (VITA Zahnfabrik, Bad Säckingen, Germany) is a tough opaque whitish material [27,28], and its physical and mechanical characteristics have been used as references for new generations (high flexural strength of 1200–1500 MPa) [27,28]. Recent compositions with higher yttria content, while improving zirconia esthetically, sacrifice mechanical performance, making it more susceptible to breakage [29–31]. These findings suggest caution when extrapolating results from longevity research focusing on older materials [7] despite promising RCTs results [32]. The bonding ability of zirconia is conditioned by airborne particle abrasion and primers or adhesives containing 10-methacryloxydecyl dihydrogen phosphate (MDP) [1,33].

Retention of restorative materials depends on the quality of the adhesive joint, which determines the bond quality at different interfaces [3]. The interface between the cement and dental tissue is essential, and the connection between the cement and the surface of the restorative material also plays a crucial role [3,34,35]. This process involves adhesion and cohesion [35–37], the first between substrates and the second within each substrate. CAD-CAM restorative materials require a multistep bonding procedure, and the specific bonding strategy for each material is determined based on its composition [1,3,20,38,39].

Characterizing the adhesive interface before adhesion, during function, and after failure is helpful for investigations and remains a significant challenge [36]. The surface treatment of each CAD-CAM material and the luting resin affect the adhesion bond strength. Therefore, a specific adhesive cementation protocol is required for each pair of materials to achieve the highest bond strength [1,40,41]. The adhesive strength or efficacy is influenced by the amount of light transmitted through the resin-matrix composite cement, which in turn is influenced by the size, content, microstructure, and shape of the inorganic filler particles.

A decrease in the degree of conversion negatively affects the physical and mechanical properties of resin-matrix composites [42]. Optimal light-curing parameters result in a low release of monomers and minimal toxicity to the dentin-pulp complex, mucosa, or periodontal tissues [34,43,44]. This aspect is pertinent because the release of these monomers must be added to that released from the restoration itself whenever a resin-based CAD-CAM material is used, except for Vita Enamic (ENA) [45], probably because of its particular structure. For these reasons, a dual-cured adhesive cement, RelyX Ultimate (RU) (3M ESPE, Seefeld, Germany) with a 3-steps adhesive strategy under photoactivated polymerization was used to assemble the experimental model [36,46,47]. Advances in adhesive dentistry and technology have expanded the possibility of using resin-bonded bridges (RBB) with alternative preparation designs and materials [48,49].

This study aimed to test a hybrid ceramic as an adherend for shear bond tests in an experimental specimen model. In parallel, the model was used to evaluate the mechanical behavior of four materials, of which three CAD-CAM monolithic ceramics, potential materials to rehabilitate clinical maxillary lateral incisor agenesis situations. The null hypotheses were that the hybrid ceramic was not a mechanically suitable adherend for shear bond tests and that no differences would be found in the mechanical behavior between the CAD-CAM monolithic ceramics.

2. Research Significance

To the best of our knowledge, this experimental model is innovative because it uses an industrially produced material as an adherend from which a uniform composition is expected, unlike what happens with biological materials. Its hybrid constitution gives it a mechanical behavior that is hypothetically similar to that of a human tooth [22]. This makes it a candidate adherend for future adhesive strength tests of dental materials, at least in preliminary studies. This experimental model identified significant differences between the restorative materials. This would overcome the ethical constraints and result biases inherent in the use of biological materials.

3. Materials and Methods

The primary materials used in this study are listed in Table 1.

Table 1. General description of the materials used in this study, their compositions, and manufacturers.

Material	Name	Code	Composition	Manufacturer
CAD-CAM Ceramics	VITA Enamic	ENA	86% feldspar ceramic: SiO_2 58%–63%, Al_2O_3 20%–23%, Na_2O_9–11%, K_2O_4–6% by weight, 14% polymer by weight: TEGDMA, UDMA	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA Suprinity	SUP	Zirconium oxide 8–12, silicon dioxide 56%–64%, lithium oxide 15%–21%, various > 10% by weight	VITA Zahnfabrik, Bad Säckingen, Germany
	VITA 3Y-TPZ	Y-ZT	Zirconia reinforced with 3% Yitria	VITA Zahnfabrik, Bad Säckingen, Germany
Resin-matrix restorative composite	PROCLINIC EXPERT Nano Hybrid composite	RES	22.5% weight, multifunctional methacrylic ester; 77.5% weight, inorganic filler (40 nm–1.5 microns).	SDI Limited, Burnston, AUS
Resin-matrix composite cement	RelyX Ultimate	RU	MDP phosphate monomer, dimethacrylate resins, HEMA, Vitrebond™ copolymer filler, ethanol, water, initiators, silane	3M Oral Care, St. Paul, MN, USA
Etching agent	VITA ADIVA Cera Etch	HF5	Hydrofluoric acid 5%	VITA Zahnfabrik, Bad Säck ingen, Germany
Ceramic primer	Monobond Plus	MB	50%–100% ethanol, disulfit methacrylate, ≤2.5% phosphoric acid di methacrylate, ≤2.5% 3-trimethoxysilylpropyl methacrylate	Ivoclar Vivadent AG, Schaan, Liechtenstein
	VITA ADIVA C Primer	CP	Solution of methacrylsilanes in ethanol	VITA Zahnfabrik, Bad Säck ingen, Germany
Adhesive system	Scotchbond Universal adhesive	SB-U	MDP, Bis-GMA, phosphate monomer, dimethacrylate resins, HEMA, methacrylate-modified polyalkenoic acid copolymer, filler, ethanol, water, initiators, silane-treated silica	3M Oral Care, St. Paul, MN, USA

VITA Enamic hybrid ceramic (ENA) blocks were used as base adherents for mechanical tests. The idealized testing protocol is shown in Figure 1. Adhesive protocols and equipment accessible in a clinical context were used instead of sophisticated equipment or chemically aggressive but efficient adhesive protocols frequently found in the literature [1]. Nevertheless, standardization was guaranteed, and a single clinical expert performed all the procedures.

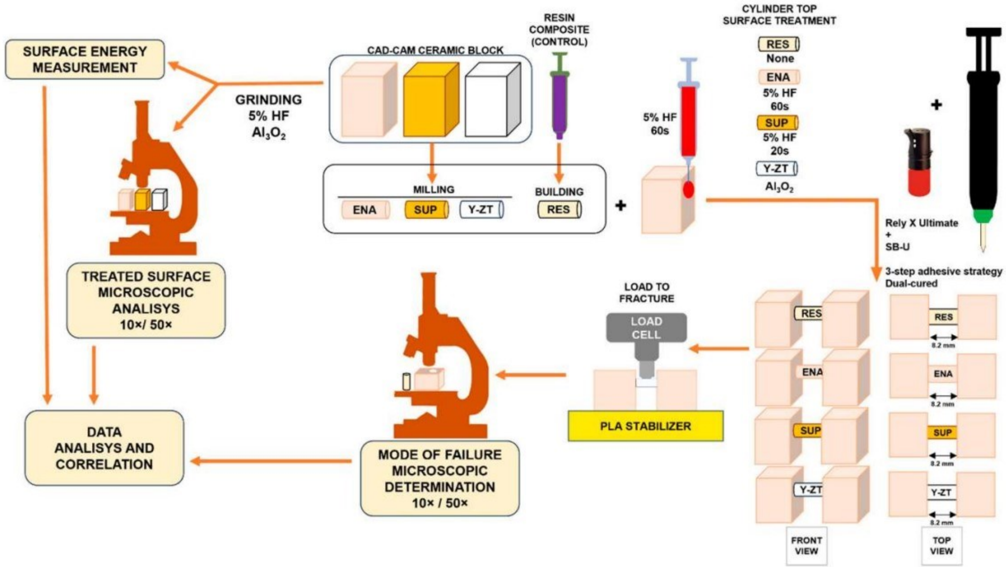

Figure 1. Comprehensive scheme of the experimental protocol workflow. ENA, Vita Enamic; HF, hydrofluoric acid; PLA, polylactic acid; SB-U, Scotchbond Universal adhesive; SUP, Vita Suprinity; Y-ZT, Vita zirconia.

3.1. Preparation of the Bases Adherend

After removing the metallic support pin from the ENA ceramic block (Figure 2A,B), the superficial gloss was removed by dry grinding to simulate the removal of the aprismatic enamel or external fluorohydroxyapatite layer. A coarse finishing disk (Soflex Disc Pop-On, 3M, Saint Paul, MN, USA) mounted in a low-speed handpiece set at 20,000 rpm and attached to the dentist chair at an angle of ±45° with the surface of the block was used. The applied force was driven by hand, as in a clinical setting, by the same restorative dentist (single operator) with >30 years of clinical experience. A new disk was used for each block with eight grinding repetitions. A 20-s oil-free air/water spray removed the debris. The prepared blocks were shuffled to ensure randomization and operator blinding.

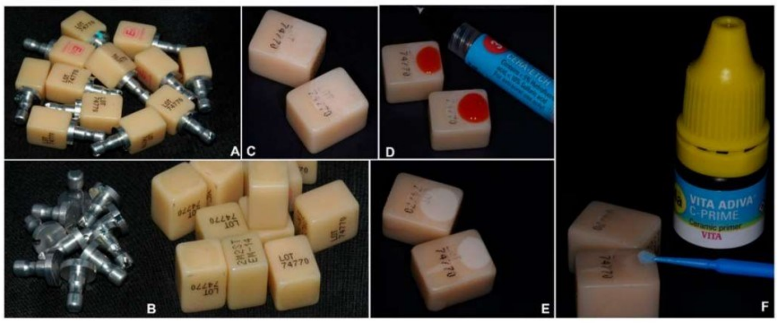

Figure 2. Vita Enamic blocks and surface treatment in the control group (RES). (**A**) before and (**B**) after support pin removal; (**C**) immediately after grinding; (**D**) during the hydrofluoric acid conditioning; (**E**) whitish conditioned and dried surface; (**F**) during the ceramic primer application, as recommended by the manufacturer.

The bonding surface of the ENA block was prepared for bonding following the sequence shown in Figure 2C–E and Figure 3. For standardization, only 4.9% (5%) hydrofluoric acid etching gel from the VITA ADIVA kit (HF5) (Vita Zahnfabrik, Bad Säckingen, Germany) was used to etch all acid-sensitive surfaces involved in the study (20 s, SU group; 60 s, ENA group), according to the manufacturer's instructions. The blocks were etched in pairs to prevent over-etching, and the etching time was controlled using a stopwatch. The treated surfaces were thoroughly cleaned using oil-free water spray for 20 s and then dried using oil-free compressed air for 10 s. The hybrid ceramic was primed with Vita ADIVA C-Primer (Vita Zahnfabrik, Bad Säckingen, Germany) in the control group (Figure 2F), and with a universal silane-containing primer (Monobond Plus, Ivoclar Vivadent) in the other groups [39,50] (Figure 3). Primers were applied using a microbrush and allowed to react for 60 s. If not completely dried after 60 s, air-drying was performed using an oil-free spray.

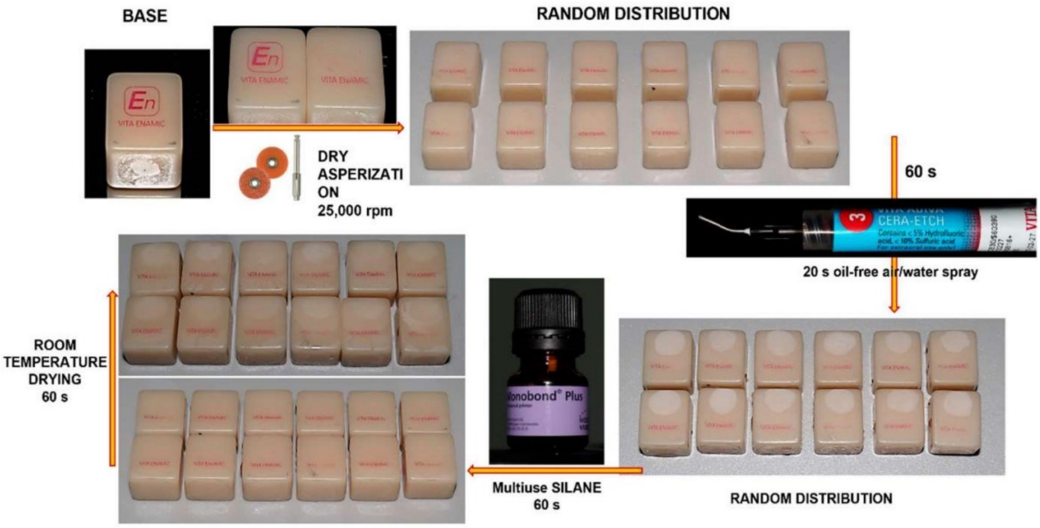

Figure 3. Sequence of the protocol for preparing the specimen bases for the groups ENA, SUP, and Y-ZT.

3.2. Preparation of the Cylinders

Monolithic ceramic cylinders (base diameter, 3.88 mm; length, 8.2 mm) (Abase = $\pi \times r^2 = 12.19$ mm^2), designed with EXOCAD software (Exocad GmbH, Darmstadt, Germany) and fabricated using a CAD-CAM inLab milling machine (Dentsply/Sirona, Charlotte, NC, USA), were produced for each ceramic material (n = 18) (Figure 4). Cylinders of the same dimensions, made of a PROCLINIC EXPERT resin-matrix nanohybrid composite (RES) (SDI Limited, Burnston, Australia) (control group), were manually manufactured using a polycarbonate cylinder template. All cylinders were checked at 10× magnification for cracks, surface discontinuities, and air bubbles and voids in the specific case of the manufactured cylinders.

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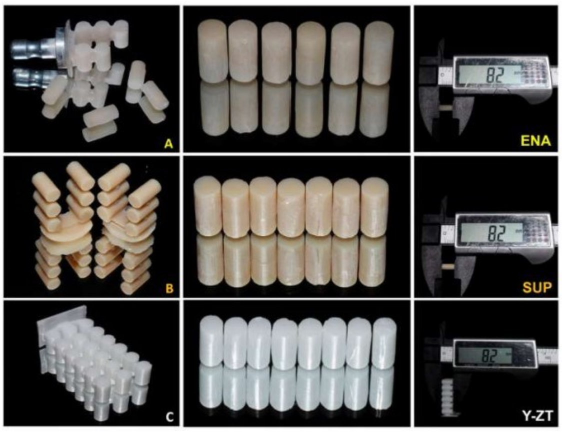

Figure 4. Fabrication and calibration of the CAD-CAM monolithic ceramic cylinders. (**A**) immediately after milling, (**B**) after being cut and regularized, and (**C**) after testing length calibration.

Cylinders considered appropriate for testing were selected (RES, SUP, Y-ZT, n = 5; ENA, n = 6) for bonding with RelyX Ultimate (RU), according to the manufacturer's instructions (Figure 5). The bonding procedures were performed immediately after each surface-conditioning method to avoid surface contamination.

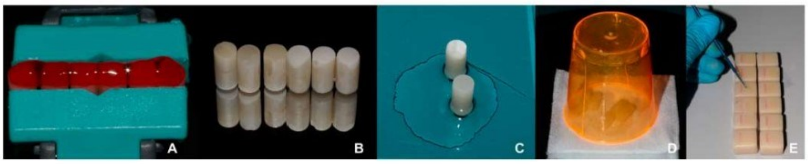

Figure 5. Cylinders and blocks in preparation for adhesion. (**A**) cylinders being conditioned; (**B**) unconditioned (3 on the left) and HF5 conditioned cylinders (3 on the right); (**C**) cylinders immersed in Monobond Plus for 60 s; (**D**) cylinders protected from daylight after adhesive system application; (**E**) adhesive system application on the blocks.

3.3. *Specimens Assembling for Shear Strength Test*

To allow standardization during specimen assembly, a silicon mold was prepared to accommodate the blocks and allow the exact height of the cemented cylinder between the blocks (Figure 6A–E). Two blocks sustained in a plastic holder by a metallic pin were inserted into a silicone ice cube mold filled with silicone putty. An extra 0.3 mm space was calculated relative to the cylinder length for easy cylinder insertion after cement application on the tops (Figure 6E).

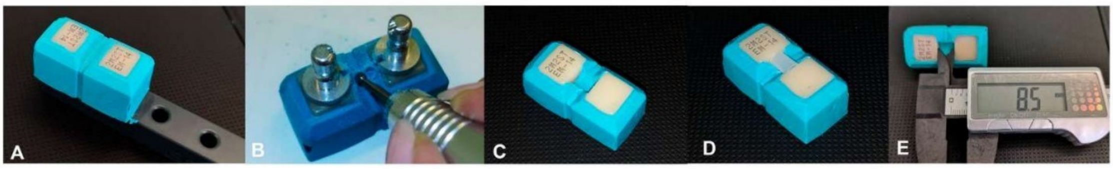

Figure 6. Steps for silicone mold production. (**A**) silicone after setting; (**B**) making the groove to fit the cylinder. Performed with a bladed round drill mounted on a handpiece at low speed; (**C**) detail of the groove definition; (**D**) polycarbonate cylinder template accommodated in the groove for calibration; (**E**) confirming the intended length between the blocks.

The excess cement was immediately removed using a microbrush. A constant pressure (0.5 kg) was applied during cement polymerization using a pinch spring (Figure 7A–C). The interfaces were light-cured for 10 s through each block and then in the middle of the cylinder for a total of 30 s using an Elipar S10 curing unit (1200 mW/cm^2; 3M ESPE) within the accepted procedure [30]. Radiant exposure was ensured by prior calibration of the light-curing device using a radiometer. The compressive force was maintained for 10 min, leaving the material to self-cure.

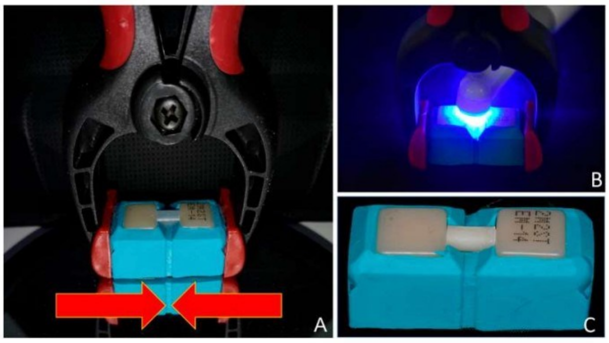

Figure 7. Constant compression for component adaptation. (**A**) during the 10 min; (**B**) detail of the photopolymerization step through the cylinder; (**C**) after polymerization and before mold removal.

Any residual cement was removed using a fine-point sickle scaler (SM 11; Hu-Friedy Co., Chicago, IL, USA). The bonded specimens were stored in saline water for 48 h at 37 °C before the SBS test.

3.4. Mechanical Characterization of Adhesive Joints

To avoid bending during testing, CAD-CAM technology creates a polylactic acid (PLA) base using free-design software and a home-mounted 3D printer. This material was selected because of its properties (environment-friendly option, low melting point (can be printed at lower temperatures and with less energy), ease of use, minimal post-processing, good surface finish, and stiff material) [51]. The details are presented in Figure 8.

Figure 8. Steps of the polylactic acid (PLA) base design and fabrication. (**A**) design steps; (**B**) PLA coil; (**C**) PLA base in the printing process; (**D**) PLA base just printed.

3.5. In Vitro RBB Materials Adhesive Joint Mechanical Characterization

The specimens of the three CAD-CAM monolithic ceramics, potential candidates for RBB to rehabilitate one missing anterior tooth, were mechanically assessed under load displacement of 0.2 mm/min (Instron–Universal tensile machine) (Figure 9). Load-displacement curves were recorded during the mechanical test. The maximum load in the test was used to identify the experimental RBB setting that supported the highest shear stress and the highest shear stress supported by the adherend before cohesive failure.

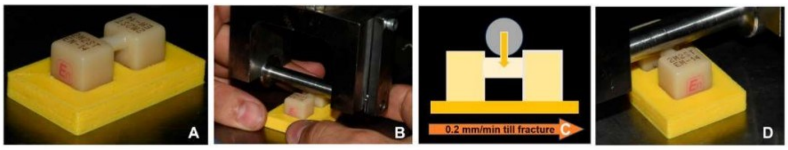

Figure 9. Specimen mounted on the polylactic acid (PLA) base ready for mechanical testing. (**A**) specimen inserted in the PLA base; (**B**) specimen being positioned on the platform; (**C**) basic scheme of the test; and (**D**) initial contact with the specimen and data registration.

3.6. Surface Energy Measurements

The surface energy of each CAD-CAM ceramic by treatment surface was measured to be correlated with the shear strength. The most commonly used surface treatments in the literature were chosen to characterize the surface energy of three CAD-CAM ceramics: grinding, hydrofluoric acid (5%), and aluminum oxide sandblasting [1,34,52].

The measurement protocol followed industry-standard methodology [37]. The surface energy (SE) for each surface treatment was calculated based on the mean of three evaluations for each liquid, using a contact angle goniometer (OCA 15, DataPhysics Instruments GmbH, Filderstadt, Germany). Contact angle measurements were performed under ambient conditions using three different liquids: water (polar liquid), ethylene glycol 55% (polar liquid), and n-hexadecane (nonpolar), following the OWRK method [35]. Figure 10 shows the SE determination after block grinding.

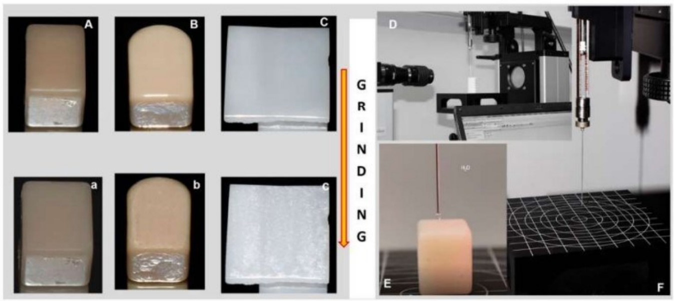

Figure 10. Substrates and equipment used for surface energy determination. (**A**,**a**) Enamic; (**B**,**b**) Suprinity; (**C**,**c**) Y-ZT blocks, as provided and after grinding; (**D**) Y-ZT block positioned for measurements; (**E**) 1 µL of water dropping on a ground Enamic block; and (**F**) detail of the reference platform and injection system.

For only grinding and hydrofluoric acid, the protocols for surface treatment were the same as in subSection 3.1. (Preparation of the base adherend). For the sandblasting surface treatment, the blocks were air-abraded at 0.20 MPa, for 10 s, with 50 µm alumina (Al_2O_3) particles. The nozzle was kept perpendicular and as perpendicular as possible to the surfaces of the blocks (angle between 80° and 90°) at a distance of 10 mm. Air abrasion was performed with erratic circular motions to ensure an even application of the AIRSONIC Alu-Oxyd powder (Hager-Werken and AZDENT sandblaster, Duisburg, Germany).

3.7. Adhesive Joint Fractography

After SBS testing, the failed specimens (block and cylinder) were inspected at a magnification of 50× and 100× using a digital microscope (AmScope Industrial Inspection, Microscope, United Scope LLC, Irvine, CA, USA). For the mode fracture classification, all components were registered as follows: adhesive fracture (bond failure at the interface between the adhesive and restorative material, even if present in small amounts), cohesive fracture in the block (fracture occurring entirely within the block structure), cohesive fracture in the cylinder (fracture occurring entirely within the restorative material), and mixed when the adhesive and cohesive modes coexisted in the central area of any interface.

3.8. Data Analysis

All data were analyzed to verify the achievement of the proposed goals. The mean load to fracture (N) and shear stress (MPa) with standard deviation (SD) were calculated for each group. A meta-analysis was conducted using the type of CAD-CAM restorative material to evaluate the shear stress between materials after calculating the difference between means and effect sizes (random-effects model; $\alpha = 0.05$; 95% CI; Z-value = 1.96). The failure mode was determined by microscopic observation and was correlated with the maximum load to fracture of the specimens. A radar graph correlates the surface energy with the load to fracture.

4. Results

Mechanical Tests

The mean shear stresses (MPa) calculated for each group are listed in Table 2. RES (69.10 ± 24.58 MPa) > Y-ZT (18.48 ± 12.12 MPa) > ENA (18.38 ± 8.51 MPa) > SUP (11.44 ± 4.04 MPa). The SUP (n = 1) and Y-ZT (n = 2) groups showed pre-test adhesive failure.

Table 2. Shear strength by mean and standard deviation in Newtons and MPa.

Groups		Failure Load			Shear Stress	
		n	Mean (N)	SD (N)	Mean (MPa)	SD (MPa)
Resin-matrix Composite		5	843.07	299.82	69.10	24.58
Rely X Ultimate	VITA Enamic	6	224.27	103.82	18.38	8.51
	VITA Suprinity	5	139.56	48.99	11.44	4.02
	VITA Y-ZT	5	225.40	147.88	18.48	12.12

SD, standard deviation; N, newtons; MPa, megapascals.

Figure 11 shows the behavior of the samples under load, and Figure 12 shows the forest plot of the shear stress by restorative material.

Despite the specimens being assembled using the same procedure, the SUP and Y-ZT groups exhibited inconsistent behavior before and during loading. The adhesion strength was material dependent. Surprisingly, the RES group performed the best, reaching mean values more than four times higher than those of the second-best ENA group.

As shown in Figures 13 and 14, the observation of the fractured specimens reveals the different mechanical behaviors of the assessed ceramics. From the observations in Table 3, failed adhesion is the unique failure mode for the Y-ZT group. The unique failure mode was cohesive in the RES group, either in the cylinder or the base, and sometimes simultaneously. Figure 15 shows a comprehensive schematic of the failure mode.

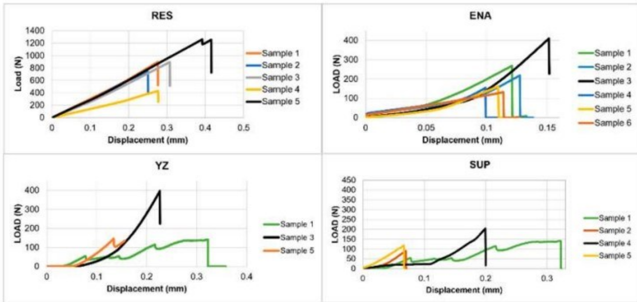

Figure 11. Graphic representation of specimen behavior under load of the control (RES), ENA, SUP, and Y-ZT groups.

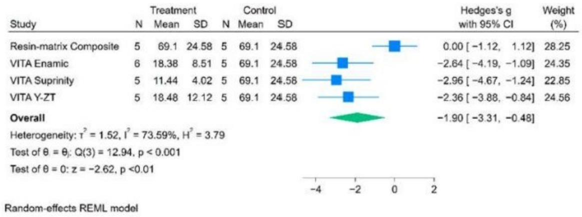

Figure 12. Forest plot of shear stress by restorative material.

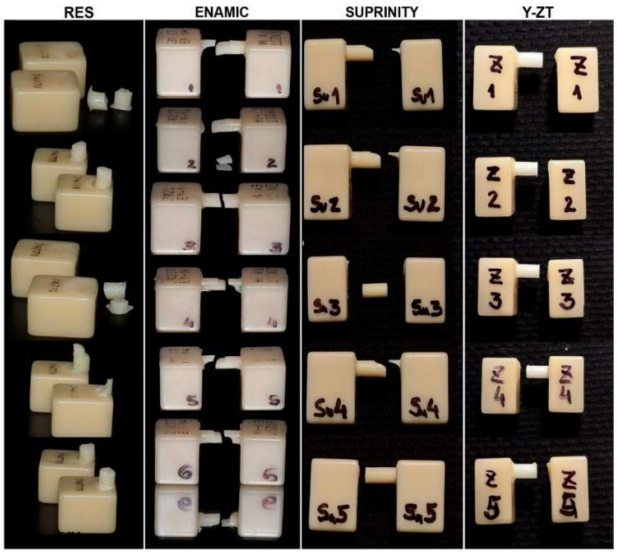

Figure 13. Fractured specimens after loading to fracture by shear forces grouped by type of material.

Table 3. Mode of failure observed in adhesive interfaces between the block and cylinder.

GROUP	Type of Failure							
	Interface 1		Interface 2		Base 1	Base 2	Cylinder	MIX
	AD	C	AD	C	C	C	C	
VITA Enamic	x						x	x
VITA Enamic							x	
VITA Enamic							x	
VITA Enamic							x	
VITA Enamic	x						x	x
VITA Enamic							x	
	Interface 1		Interface 2		Base 1	Base 2	Cylinder	
	AD	C	AD	C	C	C	C	
VITA Suprinity			x				x	x
VITA Suprinity			x				x	x
VITA Suprinity	x		x					
VITA Suprinity			x				x	x
VITA Suprinity	x							
	Interface 1		Interface 2		Base 1	Base 2	Cylinder	
	AD	C	AD	C	C	C	C	
VITA Y-ZT			x					
VITA Y-ZT			x					
VITA Y-ZT			x					
VITA Y-ZT	x							
VITA Y-ZT			x					
	Interface 1		Interface 2		Base 1	Base 2	Cylinder	
	AD	C	AD	C	C	C	C	
Nanohybrid Resin					x	x	x	
Nanohybrid Resin							x	
Nanohybrid Resin					x	x	x	
Nanohybrid Resin							x	
Nanohybrid Resin							x	

AD, adhesive failure; C, cohesive; Mix, mixed failures.

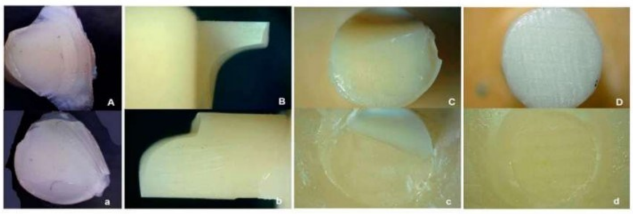

Figure 14. Examples of the mode of failure. (**A**,**a**) cohesive in the base adherend (RES_1); (**B**,**b**) cohesive in the cylinder (ENA_5); (**C**,**c**) mixed (SUP_4); (**D**,**d**) adhesive (Y-ZT_2).

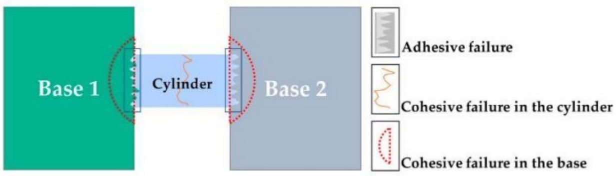

Figure 15. Comprehensive scheme of the mode of failure.

From the data obtained from the failure mechanism and surface energy of the different materials evaluated (Table 4 and Figure 16), no correlation was found between these parameters, indicating that the intrinsic chemical composition of the restorative material and its interaction with the coupling agent were the main factors affecting the mechanical behavior. Relative to the effect of the surface treatment on the CAD-CAM monolithic ceramics (Figure 17), the three treatments modified the surface of the ENA; the SUP was markedly altered by conditioning with HF 5% for 60 s and only slightly by sandblasting with AL_2O_3 50 µm, and Y-ZT was unaffected by HF 5%. These findings confirmed the data reported in the literature.

Table 4. Surface energy of the tested CAD-CAM monolithic ceramics.

	Only Grinding		
	ENAMIC	**SUPRINITY**	**Y-ZT**
Contact angle (°)	0.0	0.0	0.0
	45.9–41.0	21.5–21.6	37.5–38.2
	773–72.7	44.0–39.0	58.0–57.2
Surface Energy (mJ/m^2)	37.2	54.5	44.1
	HF 5% conditioning—60 s		
	ENAMIC	**SUPRINITY**	**Y-ZT**
Contact angle (°)	0.0	0.0	0.0
	23.6–22.8	0.0	50.1–48.6
	86.6–85.3	0.0	57.4–54.6
Surface Energy (mJ/m^2)	37.2	68.6	43.2
	Sandblasting AL_2O_3 50 µm		
	ENAMIC	**SUPRINITY**	**Y-ZT**
Contact angle (°)	0.0	0.0	0.0
	15.0–9.0	0.0	44.0–42.5
	60.7–55	0.0	60.0–59.0
Surface Energy (mJ/m^2)	46.9	68.6	42.4

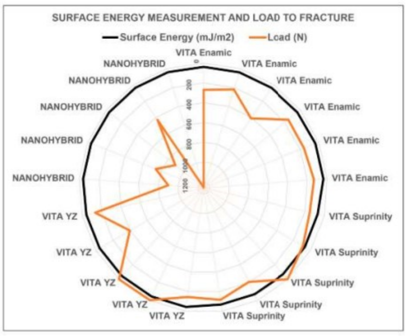

Figure 16. Radar graphic with compared mechanical performance related to the highest measured surface energy by type of CAD-CAM monolithic ceramic.

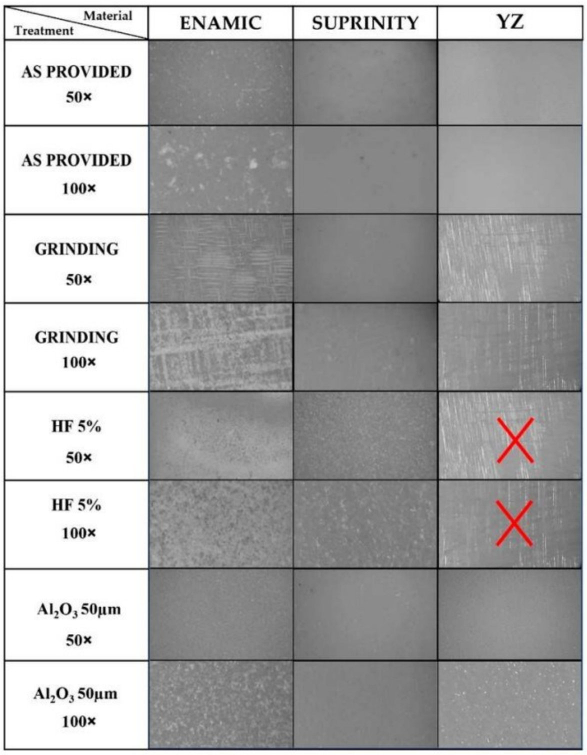

Figure 17. Microscopy observation (50× and 100× ampliation) of the CAD-CAM ceramics after different surface treatments as provided by the manufacturer, ground by coarse disk, 5% hydrofluoric acid for 60 s (HF 5%), aluminum oxide blasting (Al_2O_3 50 µm). The red cross identifies a null effect.

The crossing of microscopy and surface energy data shows that HF 5% is a suitable treatment to prepare the surface of SUP for adhesion if we only consider the microscopic interlocking between the restorative material and adhesive cement. Other materials depend on chemical reactions.

5. Discussion

The main objective of this study was to evaluate the possibility of using a standardized artificial material as a base adherent for the shear bond strength tests of restorative materials. Taking advantage of this objective and because the behavior of this material (ENA) for this purpose was unknown, CAD-CAM ceramics, from which different performances in shear bond strength testing were expected, were tested in parallel to validate the mechanical behavior of the adherend. Based on the results, the null hypothesis that the Vita Enamic hybrid ceramic was not mechanically a suitable adherend for shear bond tests was rejected, as this material withstood load forces up to 1142.89 N corresponding to an adhesive stress of 103.00 MPa. The other null hypothesis, that no differences would be found in the mechanical behavior between the CAD-CAM monolithic ceramics, was also rejected, as significant differences were found ($p < 0.01$). The meta-analysis conducted relative to different materials revealed substantial heterogeneity of results across groups due to heterogeneity rather than sampling error, with an $I^2 = 73.59\%$ of total variation and a $H^2 = 3.79$ variance between studies ($p < 0.01$).

The number of specimens used in this study reflects the surface irregularities due to manufacturing, as more than half of the cylinders were not considered suitable after 10x magnification visual inspection despite the previous calibration of the milling equipment. If the purpose is to manufacture an authentic restoration, this issue should be assessed carefully [53,54] and visual inspection with magnification before delivery should be encouraged. Nevertheless, it was not considered a real constraint for the experimental purpose, as the adherend was a homogeneous industrial material subjected to standardized surface treatment for every experimental condition, with an expected good adhesive if combined with Rely X Ultimate cement [46]. In contrast, the materials used in the cylinders were expected to differ according to the manufacturer's datasheets [25,55,56].

In this experimental design, a silicone mold was used for stabilization and standardization during the assembly. The base in PLA, because of its physical characteristics [51], ensured stabilization during mechanical tests and no flexion of the specimen, although the specimen was expected to be stable when standing alone. A silane primer was applied to the adherend surface to enhance adhesion by a chemical reaction with the polar component of the ENA structure [50,57].

Rely X Ultimate was selected based on literature [36] and parallel research [58]. The cement was used in a mixed-cure protocol (light-cure for 30 s, followed by self-cure for 10 min). To test the adhesive performance of cement was not an objective of this study. However, a control group photoactivated for only 2–3 s and left in a chemical cure for 6 min (self-adhesive mode) would be interesting to highlight the influence of chemical interactions on the success of the adhesive interface according to the cylinder material, despite the fact that the performance of this type of cement is enhanced by photopolymerization [36].

Vita Enamic was the most accessible material to handle. Vita Suprinity was very brittle in both the pre-sintered and sintered states. Polycrystalline zirconia (Vita Y-ZT) was accessible for milling, but it was almost impossible to separate the cylinders after the block had been sintered, with the destruction of several diamond points in the process. In future studies, we recommend separating cylinders before sintering. Resin-matrix composites (RES) are easy to handle; however, the possibility of including air bubbles in the cylinder upon production was a concern. Given the unexpected performance of the RES cylinder, not having determined the ultimate strength of this material is a limitation of this study, because it would have been interesting to compare it with data relative to the other materials used.

The correlation between adhesive stress and failure mode confirmed that the limitation of experimental Y-ZT RBBs lies in the success of adhesion, which agrees with the results of previous studies [32,59]. In fact, despite being the toughest material, the Y-ZT group, if the failed specimens are excluded, achieved mechanical performance similar to the ENA group (18.48 ± 12.12 MPa and 18.38 ± 8.51 MPa, respectively), which has a toughness about 8 times lower [55,56]. The exclusive adhesive failure in the Y-ZT group, including pre-test failures, reinforces the need for an easily replicable and efficient adhesion protocol when working with this type of material [1], especially in the case of a minimally invasive one-retainer anterior RBB, which does not have additional macromechanical retention [32,59].

Despite several searches of the literature and thousands of articles found related to adhesion, namely relative to zirconia [60], no studies were found that would allow for a comparison of the results of this study with other existing ones. This is due to the lack of comparable adhesive protocols or adherents, which agrees with a recent meta-analysis that identified 686 protocols to adhere 37 different CAD-CAM blocks [1], but also with the fact that, frequently, results are not available in MPa for evidence-based comparisons. Some studies have tested this type of CAD-CAM ceramic or adhesive cement. However, these studies did not use them simultaneously, nor did they evaluate them with a similar experimental setting to that of the current study, as CAD-CAM ceramics are often tested in the form of a one-piece fixed crown subjected to catastrophic fracture or pull-out tests. Other studies have evaluated CAD-CAM ceramics adhered to a cement cylinder or as a block adhered to another block.

This limitation reinforces the importance of this study because the experimental setting approaches a clinical situation of a minimal invasive resin-bonded bridge. It also showed that an industrial material could be used, at least in preliminary tests, as an adherend in shear strength tests of CAD-CAM restorative materials. This type of adherend allows for standardization and overcomes the existing constraints found in the use of biological substrates.

6. Recommendations for Future Research

Considering the potential of the tested adherend, experimental models to evaluate the shear resistance of cement with different adhesive strategies are recommended.

With CAD-CAM materials in rapid evolution, namely, those produced by addition, the use of this type of adherent could facilitate a quick and standardized evaluation of their adhesive strength, allowing easy comparison with existing CAD-CAD monolithic materials, for which there is already some scientific evidence.

7. Conclusions

The VITA Enamic block is a potential base adherent for SBS tests because it resists a shear load of up to 103 MPa (RES sample 5 test) in a cylinder with a double-interface connection design. Significant differences in the mechanical behavior with respect to the shear strength were identified between the tested CAD-CAM ceramics. Under the experimental conditions of this study, the SBS was not related to the surface energy of the substrates, and the failure mode was material-dependent. As a restorative material, ENA is predictable and easy to handle. The SUP was difficult to handle owing to its brittleness in both the pre-sintered and sintered states. The Y-ZT failure mode was always adhesive.

The tested CAD-CAM ceramics have sufficient adhesive strength to be used as resin-bonded bridges for permanent or interim rehabilitation, provided an efficient adhesive protocol is wisely chosen, and the need for short-term removal, equated as Y-ZT, is very difficult to remove by drilling.

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RESEARCH

Effect of the Modulation of the Adhesive Interface between a CAD-CAM Hybrid Ceramic adherend and Three Luting Cements on Shear Bond Strength: In Vitro Study

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Purpose: To evaluate a CAD-CAM hybrid ceramic as a potential adherend for shear bond tests by surface modulation and adhesion with three types of luting cement.
Materials and Methods: Panavia SA (SA), RelyX Ultimate (RU), and Vita Adiva IA-Cem (IA) cylinders adhered to VITA Enamic blocks were used. Block surface treatment was cutting or 5% hydrofluoric acid for 60s. VITA Adiva C-Prime (CP) and Monobond Plus (MB) were alternative coupling agents. Surface energy assessment (block and cement), shear bond strength (SBS), ultimate tensile strength, and fracture analyses were conducted. SA in the self-adhesive mode adhered to the only cut block was the control group (SA/0). Boxplots for SBS and forest plots by protocol were elaborated after calculating the difference in means and effect size (α =.05; 95% CI; Z-value=2.83).
Results: The RU/MB group had the best SBS score ($p < 0.001$). RU (38.45 ± 2.97 MPa) and IA (17.35 ± 2.39 MPa) performed better with MB and SA (24.35 ± 3.30 MPa) with CP. CP (24.35 ± 3.30 MPa) > MB (19.89 ± 2.23 MPa) increased the SBS of SA compared to the self-adhesive mode (SA/0, 13.21 ± 4.74 MPa). RU/CP showed inconsistent SBS. The surface energy of the substrates had no direct influence on the SBS. The polymerization efficacy of IA-Cem raised doubts. RU fluorescence was helpful for excess removal.
Conclusions: Except for SA/0, the tested combinations attained SBS values within those aimed for adhesion to tooth substrates. The coupling agent and cement affected the SBS under the test conditions. RU performed significantly better ($p < 0.001$) than the other cements with both coupling agents. MB performed better as a coupling agent, except for SA. The Enamic block is a potential adherend for SBS tests.
Keywords: bonding, Enamic, hybrid ceramic, luting cement, shear bond strength, surface energy, surface treatment

INTRODUCTION

Adhesive luting reinforces the mechanical properties of restorative CAD-CAM ceramics.[12] Still, the evidence-based efficacy of clinical protocols to bond CAD-CAM blocks is controversial[8, 39], and consensus concerning the surface treatment, etching concentration, etching time, and silane type for conventional adhesive luting, or the need for these procedures when luting a with self-adhesive resin cement, is lacking.[5, 39] Randomized clinical trials concerning this subject are almost nonexistent, and in vitro studies frequently fail comparable standardization.[8]

VITA Enamic (ENA) (Vita-Zhanfabrik, Germany) is a hybrid ceramic with a unique polymer-reinforced ceramic network[42] and exhibits properties similar to natural teeth, including strength and wear resistance.[27, 35] Commonly used in a wide range of dental applications,[6] its particular mechanical behavior makes it an attractive potential adherend for luting cement adhesion strength tests, allowing adherend standardization.

Surface energy assessment is essential for understanding the behavior of adherend and luting cements and for providing information about the related wettability of the material. The SE of CAD-CAM ceramics can be modulated to improve their bonding properties, theoretically increasing their longevity in the oral environment.[44] Grinding and sandblasting are mechanical methods used to modulate surfaces and create micro- and nanoscale surface irregularities. Acid conditioning with phosphoric acid (PA) and hydrofluoric acid (HF) can also be used depending on the substrate origin and chemistry.[39] Silanes, phosphates, and carboxylic acids are chemical compounds used as stand-alone coupling agents or incorporated into luting cement to create chemical bonds between substrates.[1, 29, 32] The optimal surface energy for adhesion depends on the type of adhesive and adherend. The adhesion efficiency between surfaces with similar energies is generally straightforward. For an adhesive that forms a mechanical bond, a high surface energy surface may be desirable, contrary to the fact that a low surface energy surface may be more receptive to chemical bonding.[44] According to the manufacturer's instructions, the ENA surface energy is equally increased by sandblasting or acid conditioning, with an increase in surface irregularities and roughness, thus improving mechanical bonding.

Based on the adhesion strategy, luting cements are divided into conventional resin cement combined with etch-and-rinse adhesive systems, self-conditioning resin cement associated with self-adhesive systems, and self-adhesive resin cements.[33] These last appeals to dentists because of their straightforward luting protocol.[33] However, randomized clinical trials focusing on their efficiency and intraoral longevity still need improvement, and existing in vitro studies lack standardization.[8] Conventional resin cement combined with an etch-and-rinse adhesive system is currently considered the reference for resin luting.[9, 20] Still, the multistep application increases the risk of contamination, with a decrease in bond strength.[25]

PANAVIA SA (SA) (Kuraray Noritake, Japan) is a self-adhesive resin cement designed to provide strong, long-lasting adhesion to a wide variety of materials, including glass ceramic, lithium disilicate, composite resin, zirconia, dentin, and enamel.[23] It incorporates a silane-like coupling agent (LCSi) with no need for a separate primer to bond glass ceramics, and an original MDP monomer (10-Methacryloyloxydecyl dihydrogen phosphate) that allows chemical reactivity with zirconia and tooth substrates.[23] The RelyX Ultimate (RU) (3M-ESPE, USA) is a natural fluorescent cement with a simple protocol for total-etch, selective-etch, and self-etch adhesion strategies.[17] The VITA ADIVA IA-CEM (IA) (Vita-Zhanfabrik, Germany) is an ultra-opaque, strongly masking, dual-curing resin cement for implant prosthetics, namely for bonding ENA crowns to titanium and zirconia abutments.[43]

The purpose of the present study was to evaluate a CAD-CAM monolithic material with a mechanical behavior similar to that of a human tooth as an adherend for shear bond tests of luting cement using different adhesive strategies. To understand the behavior of the block and cement, the surface energy, influence of the surface treatment on the adhesion strength, and failure mode were evaluated. The null hypotheses were that the VITA Enamic block is not tough enough as an adherend for luting cement shear bond tests, and that no significant difference exists in the shear bond strength (SBS) between the cements with different adhesive strategies adhered to a VITA Enamic block.

MATERIALS AND METHODS

Industrially manufactured Enamic (ENA) blocks were used as predictable adherends for luting cements. A single operator performed block preparation and adhesive procedures. The materials used in this study are listed in Table 1.

Table 1 Materials used in the study

Material	Name	Code	Composition	Manufacturer	Batch No.
CAD-CAM Ceramic	VITA Enamic	ENA	86% feldspar ceramic: SiO_2 58–63%, Al_2O_3 20–23%, Na_2O_9–11%, K_2O_4–6% by weight, 14% polymer by weight: TEGDMA, UDMA	VITA Zahnfabrik, Bad Säckingen, Germany	96070 95520
Resin composite cement	Panavia SA Cement Universal	SA	Paste A: MDP, Bis-GMA, TEGDMA, HEMA, silanated barium glass filler, silanated colloidal silica, dl-camphorquinone, peroxide, catalysts, pigments Paste B: HEMA, silane, silanated barium glass filler, aluminum oxide filler, sodium fluoride (<1%), dl-camphorquinone, accelerators, pigments	Kuraray Europe GmbH, Hattersheim, Germany	4N0174 Exp. 2025-02-28
	VITA ADIVA IA-Cem Ultra opaque	IA	Mixture of resin based on Bis-GMA, catalyst, stabilizer, pigments	VITA Zahnfabrik, Bad Säckingen, Germany	E72112960 Exp. 2023-07-31
	RelyX Ultimate	RU	MDP phosphate monomer, dimethacrylate resins, HEMA, Vitrebond™ copolymer filler, ethanol, water, initiators, silane	3 M ESPE, Seefeld, Germany	9592748 Exp. 2024-06-12
Etching agent	VITA ADIVA Cera Etch	HF5	Hydrofluoric acid 5%	VITA Zahnfabrik, Bad Säckingen, Germany	94450 Exp. 2024-09-30
Ceramic Primer	VITA ADIVA C-Prime	CP	Solution of methacrylsilanes in ethanol	VITA Zahnfabrik, Bad Säckingen, Germany	E52202576 Exp. 2024-04-30
	Monobond Plus	MB	50–100% ethanol, disulfit methacrylate, ≤2.5% phosphoric acid dimethacrylate, ≤2.5% 3-trimethoxysilylpropyl methacrylate	Ivoclar Vivadent AG, Schaan, Liechtenstein	Z01XT0 Exp. 2023-03-24

The information on the composition of the materials was obtained from the manufacturers' websites and SDS documents.
Bis-GMA, Bisphenol A-diglycidylmethacrylate; HEMA, 2-hydroxymethacrylate; MDP, 10-methacryloyloxydecyl dihydrogen phosphate; TEGDMA, triethyleneglycol dimethacrylate; UDMA, diurethane dimethacrylate

Specimen preparation

Before cementation, 37 ENA blocks were dry-cut using a circular class D107 diamond blade mounted on a professional precision mini-saw for ceramics (Proxxon KS 230; Wecker, Luxemburg, Germany) to remove the metallic supports and produce flat surfaces. This was followed by washing with tap water and an ultrasonic bath with 96% ethanol for two minutes. After air drying, the surfaces were checked for imperfections using a 5× magnification ZEISS EyeMag® medical loupe.

Twenty-eight blocks (14 × 12 × 14 mm) were randomly divided into seven groups (n=4). One group was left untouched (only cut), while the others were conditioned with 5% hydrofluoric acid for 60 s (VITA Ceramic Etch; Vita Zahnfabrik), randomized, treated with a coupling agent, and assigned to the experimental groups (Table 2). To ensure a uniform block-coupling agent interaction, the coupling agent was initially applied by active application with a microbrush, followed by droplet deposition, allowed to interact for 60 s, and then removed and dried using an air spray.

Table 2 Luting cement, subgroup, surface treatment, and coupling agent used in this study

Material	Subgroup	Surface Treatment	Coupling agent
Panavia SA	SA/0 (control)	Cut	None
	SA/CP	5% HF; 60 s	VITA Adiva C-Prime
	SA/MB	5% HF; 60 s	Monobond Plus
RelyX Ultimate	RU/CP	5% HF; 60 s	VITA Adiva C-Prime
	RU/MB	5% HF; 60 s	Monobond Plus
VITA Adiva IA	IA/CP	5% HF; 60 s	VITA Adiva C-Prime
	IA/MB	5% HF; 60 s	Monobond Plus

Surface energy assessment
Nine of the cut ENA blocks were assigned for surface energy assessment in 3 groups, according to the surface treatment [only cut, 5% hydrofluoric acid for 60 s, and 50 μm aluminum oxide particle sandblasting [erratic movements, 0.2 MPa, 10 mm and 10 s (AIRSONIC® Alu-Oxyd powder; Hager-Werken and AZDENT sandblaster)]. After randomization, the surface energy of each surface treatment was calculated based on the mean of three evaluations for each liquid, using a contact angle goniometer (OCA 15, DataPhysics Instruments GmbH, Filderstadt, Germany). Contact angle measurements were performed under ambient conditions using three different liquids: water (polar liquid), ethylene glycol 55% (polar liquid), and n-hexadecane (nonpolar).

Luting cement cylinder preparation
Luting cement cylinders were built for each protocol by injecting cement into a silicone mold with an inner diameter of 3.4 mm. A cement-specific Automix syringe was used for this purpose. Photopolymerization was performed for 10 s through the block, followed by 5 s from each remaining cylinder side, using a Bluephase G4 curing unit (1200 mW/cm^2; Ivoclar, Schaan, Liechtenstein). The cement was then set for 7 min, according to the manufacturer's instructions (Fig 1A-C). After mold removal, excess cement was carefully removed using a scalpel blade N.15 (Carl Martin, Solingen, Germany) (Fig 1D-E). The fluorescence of the cements was evaluated using an over-the-counter fluorescent light. The specimens were stored in saline solution for 48 h at 37 °C.

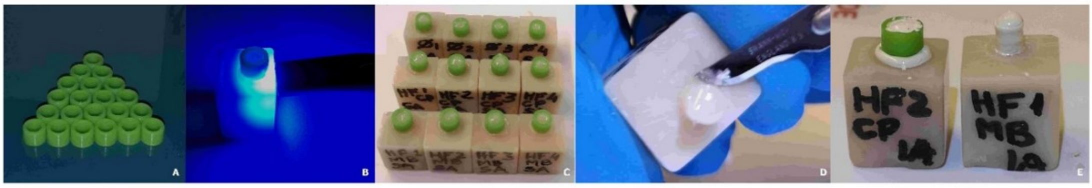

Fig 1 Silicone molds and cylinder build-up. Molds before use (A), initial photopolymerization details (B), and blocks waiting for Panavia SA cement setting (D) cement excess removal in an RU specimen, and (E) details before and after the procedure in an IA-Cem specimen

Mechanical testing and fracture surface characterization

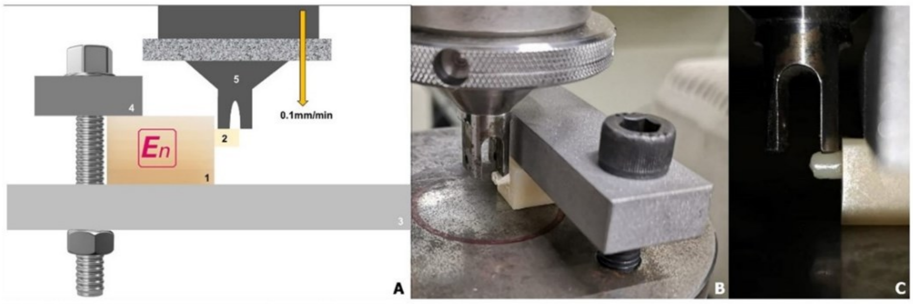

Fig 2 (A) Components designed for testing (1: ceramic block; 2: cement cylinder; 3: stationary base; 4: block stabilizer; 5: load cell and piston); (B) block stabilized on the base and specimen positioned for SBS; (C) piston positioned over the cylinder 1 mm away from the block.

The shear bond strength (SBS) was evaluated under a displacement of 0.1 mm/min until failure, and load-displacement curves were recorded using a 3400 Series Universal testing machine (Instron, Norwood, MA, US) (Fig 2).

The fracture surfaces (block and cylinder) were evaluated under 50 magnification using a digital microscope (AmScope Industrial Inspection Microscope, United Scope LLC, USA). For fracture mode classification, all components were registered when present as an adhesive fracture (even in small amounts), cohesive fracture in the block, cohesive fracture in the cement, cohesive fracture in the block with plastic deformation, and mixed whenever adhesive and cohesive modes coexisted in the central area of the interface.

Data analysis

The mean adhesive stress (MPa) and standard deviation (SD) were calculated for each group and are shown in a table and boxplot. One-way ANOVA followed by the Tukey-Kramer post-hoc test was used to compare differences (α = 0.05). Forest plot[26] by protocol shear stress after calculating the difference in means and effect size (α = 0.05; 95% CI; Z-value = 1.96) between the control protocol and all others was elaborated using a software program (Stata v18.0; StataCorp, USA).

RESULTS

General aspects

IA-Cem raised doubts about its polymerization efficacy during handling, post-polymerization inspection, and excess removal (Fig 3A-D). Despite the recommended initial photoactivation (3 s), the cement always had unpolymerized portions that adhered to silicone molds, nitrile gloves, instruments, and glass plates, which were not observed in the other cements. RU fluorescence was easily observed (Fig 4), facilitating excess removal.

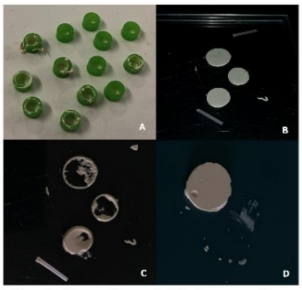

Fig 3 Details of IA-Cem after polymerization. Molds with debris removed from IA in comparison with clean molds from RU and SA (A); IA-Cem between two glass plates allowed to set for 12 h, after 60 s polymerization from one side (B), debris on the lower glass plate after cement detachment with a scalpel (C), spots of unpolymerized cement left by disk contact on the working table

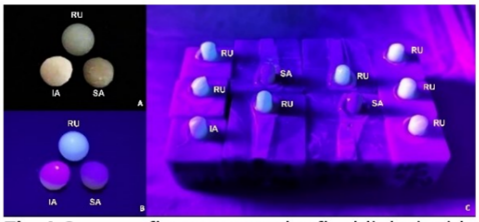

Fig 4 Cement fluorescence by flashlight incidence. Cements under daylight (A) and fluorescent light (B). RU cement shows fluorescence, and SA and IA cements show different behaviors under fluorescent light irradiation but no fluorescence (C)

Mechanical tests

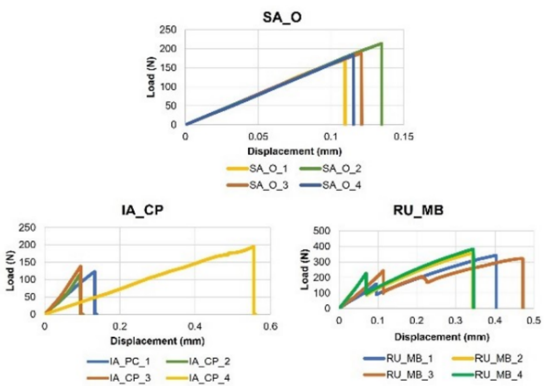

Fig 5 Specimen behavior under load to fracture, from control (SA/0), worst performant (IA/CP), and best performant (RU/MB) groups

Figure 5 shows the shear bond strength (SBS) results applied to the adhesive interface of the control, worst-performing, and best-performing groups. Table 3 shows the mean and standard deviation of SBS in the seven groups with three 3 resin cements and different adhesive strategies. The load to fracture (N) was converted to shear or adhesive stress (MPa), considering a mean bonding area of ± 9.08 mm^2 (A_{base} = π × 1.7 mm^2), to allow easier comparison with other studies.

The MB coupling agent performed better with RU (38.45 ± 2.97 MPa) and IA (17.35 ± 2.39 MPa), and the CP coupling agent performed better with SA (24.35 ± 3.30 MPa). The addition of CP (24.35 ± 3.30 MPa) > MB (19.89 ± 2.23 MPa) increased the SA shear bond compared to the self-adhesive mode (13.21 ± 4.74 MPa). In Figure 6, the boxplot of the means with standard deviation by the cementing protocol allows easy visualization of the differences.

Table 3 Mean ± standard deviation (SD) by cementing protocol, in Newtons (N) and Megapascals (MPa)

CEMENT	BLOCK SURFACE TREATMENT	COUPLING AGENT	SHEAR STRENGTH	
			Mean ± SD (N)	Mean± SD (MPa)
Panavia SA (SA/0)	Grinding	None	119.97 ± 43.05	13.21 ± 4.74
Panavia SA (SA/CP)	Hydrofluoric acid	Ceramic Primer	221.05 ± 29.99	24.35 ± 3.30
Panavia SA (SA/MB)	Hydrofluoric acid	Monobond Plus	180.59 ± 20.27	19.89 ± 2.23
Rely X Ultimate (RU/CP)	Hydrofluoric acid	Ceramic Primer	217.32 ± 114.80	23.94 ± 12.64
Rely X Ultimate (RU/MB)	Hydrofluoric acid	Monobond Plus	349.12 ± 26.94	38.45 ± 2.97
Adiva IA (IA/CP)	Hydrofluoric acid	Ceramic Primer	142.50 ± 36.50	15.70 ± 4.02
Adiva IA (IA/MB)	Hydrofluoric acid	Monobond Plus	157.50 ± 21.7	17.35 ± 2.39

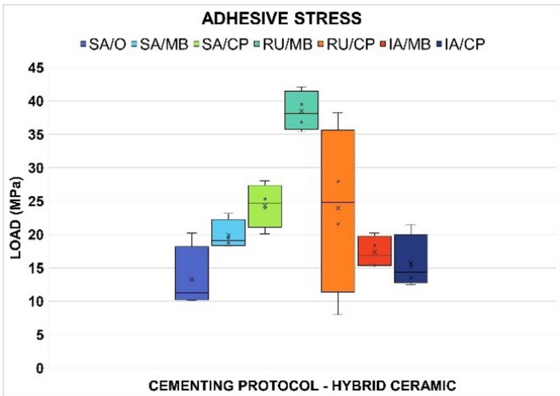

Fig 6 Boxplot of adhesive stress by cementing protocol

Surface energy assessment

Tables 4 and 5 show the surface energies calculated from the partial values obtained for the three liquids used.

Table 4 Surface energy of block, determined by contact angle measurement

	SURFACE ENERGY (mJ/m^2)		
	Grinding	5% HF	Sandblasting
VITA Enamic	37.2	37.2	46.9

Table 5 Surface energy of cements, determined by contact angle measurement

	SURFACE ENERGY (mJ/m^2)		
	RU	SA	IA
Immediately after mixing	51.89	49.6	37.96
Polymerized	38.94	37.16	42.24

Figure 7 suggests that factors other than surface energy are responsible for the different mechanical performances of the luting cements. Despite the similar surface energies of luting cements, their behaviors are dissimilar.

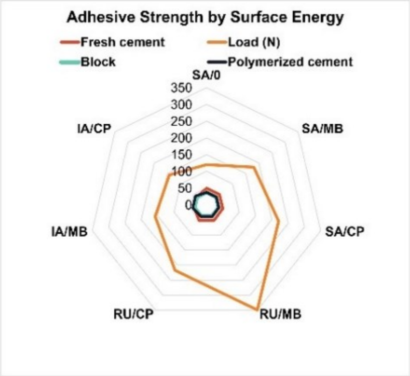

Fig 7 Radar graphic showing different mechanical performances of cement and coupling agent combinations

Fracture microscopy and fractographic analysis

Microscopic observation of the interface surfaces showed dissimilar behaviors from the different substrates according to the cement and coupling agent association with different fracture modes (Fig 8 to 10).

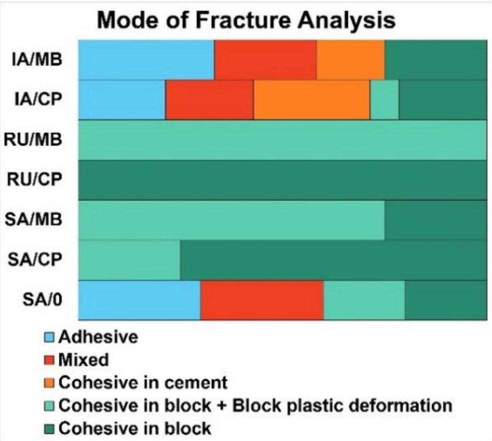

Fig 8 Mode of fracture observed in adhesive interfaces between the block and cement cylinder

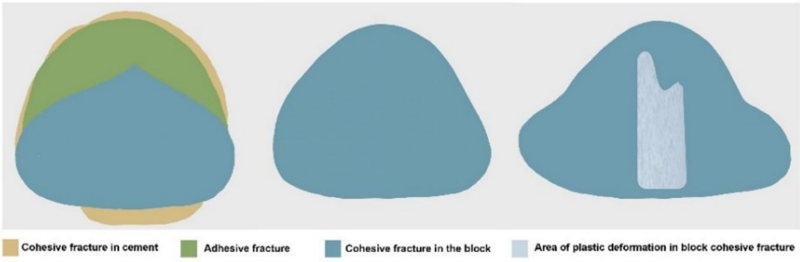

Fig 9 Simplified explanatory scheme of the fracture modes found by the study under the microscope

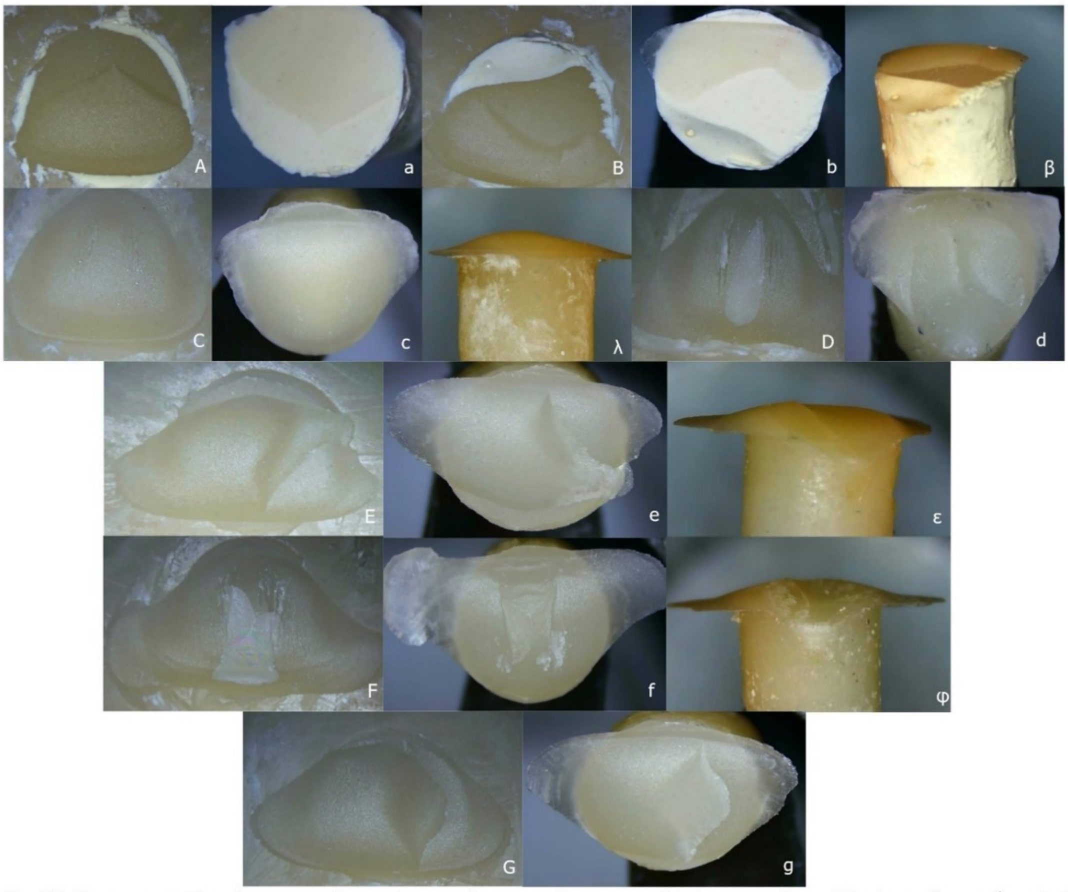

Fig 10 Representative fracture of specimens from each group with images from block surfaces (capital letters), top view of cement cylinders (small letters), and lateral view of cement cylinders (Greek letters). A, a (IA/CP)- adhesive fracture and cohesive fracture in block and cement; B, b, β (IA/MB)- adhesive fracture and cohesive fracture in block and cement; C, c, λ (RU/CP)- cohesive fracture in the block; D, d (RU/MB)- cohesive fracture in the block with plastic deformation; E, e, ε (SA/O)- cohesive fracture in the block with plastic deformation; F, f, φ (SA/CP)- cohesive fracture in the block with plastic deformation; G, g (SA/MB)- cohesive fracture in the block with plastic deformation

Statistics and meta-analysis

One-way ANOVA indicated that the bond strength was significantly different among the groups ($p < 0.001$, $F = 8.62$) (Table 6). The Tukey-Kramer comparisons indicated significant differences between RU/MB and the other cements and adhesive strategies, even with RU/CP (Table 7). The boxplot reveals a consistent behavior of RU/MB, opposing the inconsistent performance of RU/CP despite having supported higher loads than SA and IA in all adhesive strategies (Fig 6).

Table 6 One-way ANOVA analysis of variance

Source	Analysis of variance SS	df	MS	F	Prob > F
Between groups	139413.378	6	23235.563	8.62	0.0001
Within groups	56617.8508	21	2696.08813		
Total	196031.229	27	7260.41589		

Bartlett's equal-variances test: chi2(6) = 14.7202 Prob>chi2 = 0.023

Table 7 Tukey-Kramer analysis post hoc after one-way ANOVA

Tukey Kramer Multiple Comparison Procedure

Comparison	Absolute Difference	Critical Range	Result	
SA/0	SA/MB	60.62	112.42	b
SA/0	**RU/MB**	**229.15**	**112.42**	**a**
SA/0	IA/MB	37.54	112.42	b
SA/0	SA/CP	101.09	112.42	b
SA/0	RU/CP	97.36	112.42	b
SA/0	IA/CP	22.54	112.42	b
SA/MB	**RU/MB**	**168.53**	**112.42**	**a**
SA/MB	IA/MB	23.08	112.42	b
SA/MB	SA/CP	40.47	112.42	b
SA/MB	RU/CP	36.74	112.42	b
SA/MB	IA/CP	38.08	112.42	b
RU/MB	**IA/MB**	**191.62**	**112.42**	**a**
RU/MB	**SA/CP**	**128.07**	**112.42**	**a**
RU/MB	**RU/CP**	**131.80**	**112.42**	**a**
RU/MB	**IA/CP**	**206.62**	**112.42**	**a**
IA/MB	SA/CP	63.55	112.42	b
IA/MB	RU/CP	59.82	112.42	b
IA/MB	IA/CP	15.00	112.42	b
SA/CP	RU/CP	3.73	112.42	b
SA/CP	IA/CP	78.55	112.42	b
RU/CP	IA/CP	74.82	112.42	b

a - Means significant difference; b – a NOT significant difference

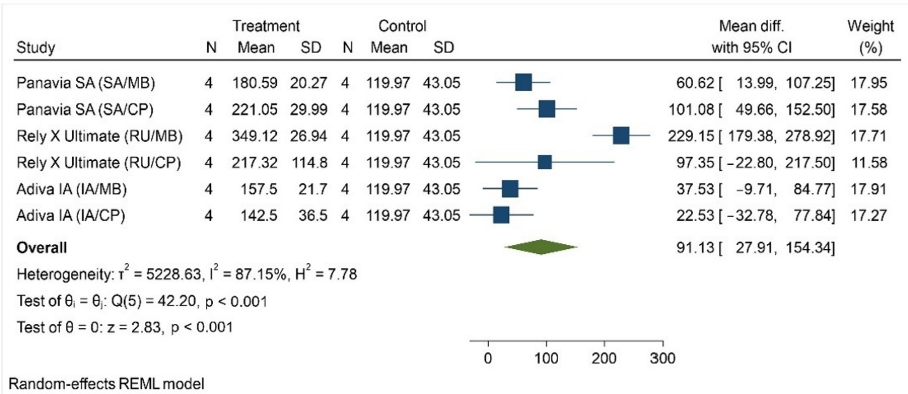

Fig 11 Forest plot of the difference in means and effect sizes by cementing protocol

From the observation of the forest plot showing the difference in means and effect size (α = 0.05; 95% CI; Z-value = 2.83) (Fig 11), despite heterogeneity, we observed a tendency toward better performance for all combinations compared to the control group ($p < 0.001$). The RU/MB combination was the best performant and had the most significant discrepancy compared with the control group ($p < 0.001$).

DISCUSSION

This study assessed the influence of a coupling agent and surface treatment on the shear strength of three luting cements with different technologies, adhered to a potencial CAD-CAM hybrid ceramic adherend. The absolute strength of the adhesive joint was used to validate this adherend for future SBS tests.

Based on the obtained results, the null hypotheses were rejected because the VITA Enamic block was sufficiently tough to support the shear bond strength tests in this experimental design, and significant differences ((α=0.05; p< 0.001) in the shear bond strength (SBS) between luting cements were identified.

Laboratory studies assessing the adhesive efficiency of luting cements often use equipment that surpasses that available in dental offices. This compromises an easy transposition of laboratory protocols to a clinical practice founded on scientific evidence.[8] To overcome this, the experimental protocol for specimen production used only equipment available in a medium-investment dental office because all technical procedures were intended to be applicable in a clinical setting. To ensure standardization, all the steps followed strict protocols and were performed by a single experienced operator.

The hybrid ceramic Enamic was selected based on its unique mechanical behavior. It has been suggested by its hardness as suitable for enamel substitution (Vickers hardness: enamel, 274.8 ± 18.1 HV; VITA Enamic, 200 HV),[11, 40] and by its flexural strength as a human dentin substitute (dentin, 80-140 MPa; VITA Enamic, 150-160 MPa).[11, 40, 42] In this study, the exclusive cohesive failure in the block occurred between 42.13 MPa and 20.09 MPa for the RU/MB and SA/CP associations, respectively, and is related to the toughness of the material. In most studies, the conversion method from Newtons to Megapascals (absolute load values by loaded area or adhesive stress) is not explicit or lacking. For this reason, the values obtained in this study were not directly comparable with those. Compared to other existing studies, the sample number was relatively low, but as the adherend was an industrial material, homogeneous by defect, based on preliminary tests, widened that number it was considered a waste of resources. In reality, the Enamic block was mechanically consistent and exhibited interesting behavior during testing, allowing us to overcome the variability of biological substrates[13, 34] and the inconvenience of ethical or sanitary retrains that emerge from using human or bovine teeth in laboratory tests.

SA cement[23] is a dual-cure self-adhesive resin cement that can be light-cured or self-cured after chemical activation, and is capable of bonding to enamel, dentin, metal alloys, and zirconia through chemical interaction with its 10-MDP component (10-methacryloyloxydecyl dihydrogen phosphate), and to porcelain, lithium disilicate, and composite resin by chemical interaction with the LCSi monomer (low-cyclic siloxane monomer).[46] Self-adhesive resin cements are self-etching materials that, ideally after mixing wet well the tooth surface, promoting demineralization due to low pH and early high hydrophilicity.[25, 37] Assuming that the hydrophobicity of a cement depends on the surface energy and also on factors such as surface roughness and chemical composition, in this study it was observed that, after curing (light and self-cure), the surface energy values of cements decreased in RU (51.89; 38.94 mJ/cm^2), SA (49.6; 37.16 mJ/cm^2), and heightening in IA (37.96; 42.24 mJ/cm^2) compared to values of fresh-mixed cement (Table 5)The literature indicates that after 24 h, the degree of conversion of RU was comparable between their curing modes, whereas that of SA was significantly lower for the self-curing mode than for the light-curing mode.[2] Regarding IA-Cem, no data were found in the literature.

In this study, the specimens were immersed for longer than those commonly reported in the literature[8] (48 h instead of 24 h) to allow more time for chemical curing owing to the polymerization problem already mentioned (Fig 3). This should not have changed the hardness of the material because, up to 7 days Enamic does not undergo significant hygroscopic changes by immersion in water, probably due to its structural ceramic network.[24]

Based on its chemistry, SA cement theoretically adheres to all materials without requiring a separate primer.[23] However, adding a coupling agent (MB or CP) was clearly beneficial for the adhesive strength of the joint between SA cement and Enamic, a find that conflicts with those found for a leucite-based glass-ceramic substrate cemented with SA.[46]

Based on the results, except for IA/CP, IA/MB, and SA/O, the adhesive strength of the adhesive interface overcame the tenacity of the Enamic block adherend, which experienced cohesive failure during testing. In Figure 10D-G, the plastic deformation of the block is feasible, a behavior that is also suggested by the trace observation in the graphics in Figure 5, with nonlinear tracing probably reflecting mechanical strain adaptation to load increment, probably dependent on the polymeric component of this hybrid ceramic.

Surface energy analysis of substrates is essential for correlating the physical behavior of materials at the interface. The contact angle measurement is a simple and quick standard method (OWRK method) providing information about the surface energy (SE) and properties of a solid material and the wetting behavior of a liquid.[30] The liquids used in this study were (1) water, to measure surface hydrophilicity or hydrophobicity, factors involved in the adhesion to a natural tooth; (2) n-hexadecane, used mainly for hydrophobic materials, as it has a low surface tension; and (3) ethylene glycol, by its low surface tension result of the polar nature, and presence of hydroxyl (OH) groups in its molecule, used mainly for materials with polar or hydrogen-bonding properties, such as metals, ceramics, and glasses.[36] In the case of luting cements, to achieve a strong and durable bond, the cement must be able to wet and penetrate the irregularities of the tooth surface, which requires higher surface energy than that of the tooth surface.

This study used a hybrid ceramic (Enamic) to simulate human teeth. The two surface treatments used on the VITA Enamic block (grinding and 5% hydrofluoric acid) induced the same surface energy (37.2 mJ/m^2), so we can conclude that for this substrate, either is acceptable. When analyzing the surface energy of the fresh mixed luting cement (RU, 51.89 mJ/m^2; SA, 49.6 mJ/m^2; IA, 37.96 mJ/m^2) relative to the shear bond strength, no direct influence was established, probably by the interference of the coupling agent, but the SBS values were higher for RU followed by SA and IA. The MB surface energy values were not found in the scientific or manufacturer literature. However, it works as an adhesion promoter by increasing the surface energy of the substrate because of its content in silane, methacrylate phosphoric acid ester, and sulfide methacrylate, to work with glass ceramics, resin-based restorative materials, metals, and some types of dental alloys. Silane-containing coupling agents were described as enhancer of adhesive strength when adhering to Enamic.[45]

Concerning the luting cement, the coupling agent and the luting cement itself seems to be more important than the relative surface energy among cements (Fig 7), as the same cement, adhered to the block, has different mean SBSs when associated with a different coupling agent or in the absence of it (RU/MB, 349.12 ± 26.94N; RU/CP, 217.32 ± 114.80N; SA/CP, 221.05 ± 29.99N; SA/MB, 180.59 ± 20.27N; SA/0, 119.97 ± 43.05N; IA/MB,157.50 ± 21.7N; IA/CP, 142.50 ± 36.50N).

ANOVA (Table 6) confirmed significant differences between the groups ($p < 0.0001$), and the Tukey-Kramer post-hoc ANOVA confirmed the insight provided by the boxplot (Fig 6). Therefore, the chemistry of the interface should be further assessed in the future. Notably, the coupling agent recommended by the manufacturer[42] for block priming was not the best performer except when associated with SA cement.

A limitation was not having a group with alumina oxide sandblasting as a surface treatment to modulate the block surface,, as this surface treatment attained the higher surface energy (46.9 mJ/m^2 versus 37.2 mJ/m^2) and has been suggested to increase the bond strength between dentine and self-adhesive luting cements.[41] It was not considered from the beginning because the manufacturer,[42] despite mentioning it as possible, based on literature, continues to recommend the 5% HF in the clinical context.[19] The use of tribochemical silica coating has also been suggested, but the findings are not consensual.[15, 16, 38] However, we must consider that HF use is more comfortable for the patient and dentist, as it does not compromise the cleanliness of the operatory field. The SE of ENA (adherend) was the same when the surface was grinded or treated with 5% HF (37.2 mJ/m^2). As a control group (SA/0), the cement was applied strictly self-adhesively, with the suspicion based on the literature[9] of worse performance compared to other protocols. A trend was observed, but the difference was significant only in comparison with RU/MB ($p < 0.0001$).

The initial light-curing time was longer than that recommended by the manufacturer (10 s + 5 s×3 instead of 2-3 s). Still, it was an option considering the possible light attenuation due to the IA opacity[18, 28] and because extending the light-curing time of cements in a clinical context has been suggested[28] to maximize mechanical properties,[10] extend restoration stability[22] and minimize cellular cytotoxicity.[3] To standardize, other cements followed the same curing protocol. In recent years, the touch-cure was introduced,[21] to improve the monomer conversion in dark or tiny exposed to curing light areas,[7] improving the bonding strength and reducing shrinkage stress, resulting in a longer-lasting restoration.[14]

The natural fluorescence of RU cement (Fig. 4) was easily visualized using a low-cost fluorescent flashlight. This optical property may help the dentist remove gingival excesses, preventing periodontal damage.[4] The IA-Cem raised doubts about the degree of conversion, because during the production of cement cylinders, after applying the curing protocol (10 s + 5 s×3) (Fig 7A) and even after 60 s of light curing followed by 12 h of self-curing, some areas remained soft and sticky (Fig 7B-D). Considering that this cement is advocated for luting crowns to implant abutments,[43] this issue is even more concerning. This problem should be addressed in future studies to safeguard clinicians. Besides the possible loosening of the restoration, a low degree of conversion allows the release of toxic monomers for the fibroblast or mesenchymal cells.[31]

CONCLUSIONS

Except for SA/0, the tested combinations attained shear bond strength values within those aimed at adhesion to the tooth substrates. The coupling agent and cement affected the SBS under the test conditions. RU performed significantly better than the other cements with both the coupling agents (MB and CP). Except for SA, the MB performed better as a coupling agent. The VITA

Enamic hybrid ceramic block is a potential support for shear tests with luting cement. SBS tests with Enamic monolithic hybrid ceramic allowed to identify differences between cements with dissimilar adhesive strategies.

CLINICAL RELEVANCE

Coupling agents improve the performance of luting cements, but are not a substitute for proper clinical techniques and tooth and restoration surface treatment. The manufacturer's instructions do not always produce the best laboratory mechanical performance of a material but should be followed until further information is provided from randomized clinical trials.

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Research

Shear bond strength of simulated single-retainer resin-bonded bridges made of four CAD/CAM materials for maxillary lateral incisor agenesis rehabilitation.

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Abstract

Objectives: Maxillary lateral incisor agenesis (MLIA), treated orthodontically by space opening, requires complimentary esthetic rehabilitation. Resin-bonded bridges (RBB) can be equated as interim rehabilitation until skeletal maturity is achieved to place an implant-supported crown or as definitive rehabilitation in case of financial restrictions or implant contraindications. Scientific evidence of the best material must be confirmed in specific clinical situations. Computer-aided design and computer-aided manufacturing (CAD/CAM) materials are promising versatile restorative options. This study aimed to identify a straightforward material to deliver interim or definitive resin-bonded bridges for non-prep tooth replacement in MLIA.

Materials and Methods: Single-retainer RBB made from CAD/CAM ceramic blocks [Vita Enamic (ENA), Suprinity (SUP), and zirconia (Y-ZPT)] and a 3D printed material (ABS) were evaluated by shear bond strength (SBS) and mode of failure, after adherence with Rely X Ultimate used in a 3-step adhesive strategy to artificial teeth.

Statistical analysis: The load to fracture (N) was recorded, and the mean shear stress (MPa) was calculated with standard deviations (SD) for each group and compared between materials using boxplot graphics. One-way ANOVA followed by the Tukey-Kramer post-hoc test was used to compare the differences ($\alpha = 0.05$). A meta-analysis focusing on CAD/CAM materials evaluated the magnitude of the difference between groups based on differences in means and effect sizes ($\alpha = 0.05$; 95% CI; Z-value = 1.96). Failure mode was determined by microscopic observation and correlated with the maximum load to fracture of the specimen.

Results: The mean ± standard deviation SBS values were ENA (24.24 ± 9.05 MPa) < ABS (24.01 ± 1.94 MPa) < SUP (29.17 ± 4.78 MPa) < Y-ZPT (37.43 ± 12.20 MPa). The failure modes were mainly adhesive for Y-ZPT, cohesive for SUP and ENA, and cohesive with plastic deformation for ABS.

Conclusions: Vita Enamic, Suprinity, Y-ZPT zirconia, and 3D-printed ABS RBBs are optional materials for rehabilitating MLIA. The option for each material is conditioned to estimate the time of use and necessity of removal for orthodontic or surgical techniques.

Keywords: 3D additive manufacturing, adhesion, CAD/CAM, maxillary lateral incisor agenesis, monolithic ceramics, shear bond strength, surface energy

Introduction

Maxillary lateral incisor agenesis (MLIA) is a prevalent non-syndromic congenital tooth agenesis that occurs bilaterally in more than half of the cases. It is frequently associated with a peg-shaped contralateral tooth if unilateral.[1,2] Occurrence in the anterior maxilla is associated with reduced maxillary sagittal growth and altered relative lower incisor position,[3] making functional post-orthodontic stabilization pertinent. Challenging MLIA treatment has valuable esthetic options, including orthodontic space opening followed by prosthetic replacement of the missing lateral incisor or space closure with canine mesialization complemented by tooth remodeling.[4-6] Single-retainer resin-bonded bridges (SRBB) are reversible, esthetic, and predictable minimally invasive restorative options for fixed interim or definitive replacement of the missing lateral incisors in cases of space-opening procedures.[5,6]

Computer-aided design/manufacturing (CAD/CAM) materials have emerged as versatile materials for esthetic restorations. However, clinical evidence-based data concerning their success and durability still need to be explored.[7,8] Furthermore, the industrial materials available for digital workflow evolve faster than the data available from research based on high-quality clinical trials.[9] Accurate knowledge from clinicians and dental prosthetics is needed to optimize and succeed in the available options.[10] In vitro studies frequently integrate equipment unavailable in clinical settings, and only some experimental protocols can be transposed directly from the laboratory to the clinical context.[9] Therefore, an experimental research design that simulates clinical conditions and uses a standardized base adherend to replace the natural tooth could help understand the behavior of materials and prostheses.

The micromechanical bond between CAD/CAM materials and teeth substrates depends on bonding systems[11] and chemical interactions that occur between functional monomers and tooth components,[12] which in turn depend on the properties of the materials, which are crucial to the success of adhesive restorations.[13]

CAD/CAM monolithic ceramics are mainly polycrystalline, glass-matrix, indirect composites, and hybrid ceramics.[14,15] Combining a low flexural modulus with a high flexural strength (150–160 MPa), the hybrid ceramic Vita Enamic (ENA) (VITA Zahnfabrik, Bad Säckingen, Germany) is a polymer-infiltrated ceramic network[14] capable of elastic deformation before failure, with a mechanical behavior similar to that of a human tooth.[16] Despite low stiffness,[17] it is quite stable under extreme acid exposure, and cyclic loading does not affect its properties.[18] Its unique polymer-based microstructure is essential for the micromechanical bond and the performance of the adhesive interface[19,20] due to a decreased crack propagation.[21] High translucency, fluorescence, and opalescence are the main characteristics of Vita Suprinity (SUP) (VITA Zahnfabrik, Bad Säckingen, Germany), according to the manufacturer. Delivered pre-crystallized, this homogeneous fine-grained (0.5–0.7 µm) glass-ceramic enriched with zirconia has a consistently high load capacity (flexural strength in crystallized state, 420 MPa). It is an interesting material for anterior resin-bonded bridges because of its esthetics, biocompatibility, and mechanical properties. Still, clinical data remain scarce, often controversial, and limited to short-term observational periods, suggesting urgent in vitro/in vivo studies assessing long-term performance.[22]

The polycrystalline ceramic Vita YZ HT (Y-ZPT) (VITA Zahnfabrik, Bad Säckingen, Germany) is a conventional 5 mol% yttria-stabilized zirconia and a reference for new generations by its physical and mechanical characteristics.[23,24] Its main characteristics are its high flexural strength (1200–1500 MPa) and opaque white appearance.[25] Recent zirconia compositions with higher yttria content, while improved esthetically, have lower mechanical performance and are more susceptible to breakage.[23,24] As the thickness, composition, microstructure, and cementing agent are crucial for the resistant tetragonal phase of monolithic zirconia,[26] caution is mandatory when extrapolating results from research focusing on the longevity of older materials.[10] Although scarce, available randomized clinical trials have promising results.[27] Meanwhile, it is accepted that the adhesive strength of zirconia depends on airborne particle abrasion and on primers or adhesives containing 10-methacryloxydecyl dihydrogen phosphate (MDP).[28]

Acrylonitrile butadiene styrene (ABS) is an affordable, lightweight thermoplastic polymer with good impact strength and abrasion resistance. Its low melting point (105°C) makes it ideal for in-office equipment. Acrylonitrile provides rigidity, resistance to chemical attack, hardness, and stability at high temperatures; butadiene confers tenacity to temperature; and styrene increases mechanical strength, rigidity, brightness, and hardness. Medical ABS (Smartmaterials 3D, Jaén, Spain) (ISO 10993-1) is a BPA-free material produced via fused deposition. It attains tensile strengths ranging from 15 to 38 MPa and an elastic modulus of 1300–1800 MPa. Differences in mechanical behavior depend on processing temperatures, printing parameters, proportions of monomers in the ABS structure, and force orientation during testing.[29]

Advances in adhesive dentistry and technology have expanded the use of resin-bonded bridges (RBB) with alternative preparation designs and materials.[30] To best predict the future clinical performance of RBBs, similar designs, and fabrication procedures following real dental laboratory and clinical procedures should be chosen.[31]

The quality of an adhesive joint is determined by the bond quality at different interfaces and the adhesive strength of the restorative materials, as in the case of RBBs. The interfaces between the dental tissue and the adhesive cement and the connection between the cement and the surface of the restorative material play essential roles.[32] In this process, adhesion and cohesion[33,34] are involved, with the first between the substrates and the second within each substrate.

Characterization of the interface before adhesion, during function, and after failure is helpful for investigations and remains a significant challenge.[34] The surface treatment of each CAD/CAM material and the luting resin influences the adhesion bond strength; therefore, a specific adhesive cementation protocol is required for each paired material to obtain the highest bond strength.[9,35]

Based on previous research,[20] a photoinitiated dual-cured adhesive cement, RelyX Ultimate (RU) (3M ESPE, Seefeld, Germany), used in a 3-step adhesive strategy, was used to adhere the experimental RBBs to an artificial tooth. This study evaluated single-retainer RBBs manufactured similarly to those for clinical application in MLIA. Three CAD/CAM monolithic ceramics and one additive-manufactured CAD/CAM material adhered to an artificial tooth with dual-cured cement were assessed for shear bond strength (SBS) and fracture mode. The null hypothesis was that no differences would be observed between the shear bond strengths of the tested materials in the tested RBB model.

Materials and Methods

The materials used in this study are listed in **Table 1**. Polycrystalline zirconia (Y-ZPT) was used as control material.

Table 1 General description of materials used in this study, their compositions, and manufacturers.

Material	Name	Code	Composition	Manufacturer
CAD-CAM Monolithic ceramics	Vita Enamic	ENA	86% feldspar ceramic: SiO_2 58–63%, Al_2O_3 20–23%, Na_2O_9–11%, K_2O_4–6% by weight, 14% polymer by weight: TEGDMA, UDMA	VITA Zahnfabrik, Bad Säckingen, Germany
	Vita Suprinity	SUP	Zirconium oxide 8–12, silicon dioxide 56–64%, lithium oxide 15–21%, various > 10% by weight	VITA Zahnfabrik, Bad Säckingen, Germany
	Vita 5Y-TPZ Color	Y-ZPT	Zirconia reinforced with 5% Yitria	VITA Zahnfabrik, Bad Säckingen, Germany
CAD-CAM 3D printed material	Medical ABS	ABS	Acrylonitrile butadiene styrene	Smartmaterials 3D, Jaén, Spain
Resin-matrix composite cement	RelyX Ultimate	RU	MDP phosphate monomer, dimethacrylate resins, HEMA, Vitrebond™ copolymer filler, ethanol, water, initiators, silane	3M Oral Care, St. Paul, MN, USA
Etching agent	Porcelain Etch Gel	PEG	Hydrofluoric acid 9.6%	Pulpdent, Watertown, MA, USA
Ceramic primer	Monobond Plus	MB	50–100% ethanol, disulfit methacrylate, ≤2.5% phosphoric acid dimethacrylate, ≤2.5% 3-trimethoxysilylpropyl methacrylate	Ivoclar Vivadent AG, Schaan, Liechtenstein
Adhesive system	Scotchbond Universal adhesive	SB-U	MDP, Bis-GMA, phosphate monomer, dimethacrylate resins, HEMA, methacrylate-modified polyalkenoic acid copolymer, filler, ethanol, water, initiators, silane-treated silica	3M Oral Care, St. Paul, MN, USA
Hydrophobic resin	Heliobond	HEL	HEMA, Bis-GMA, UDMA, initiators (camphorquinone and benzoyl peroxide), fillers (silica, glass particles, solvents (ethanol and acetone)	Ivoclar Vivadent AG, Schaan, Liechtenstein
Artificial Teeth	FRASACO Tooth	FRA	Melamine based composition	Frasaco GmbH, Tettnang, Germany

Bis-GMA, bisphenol A glycidyl methacrylate; HEMA, 2-hydroxyethyl methacrylate; MDP, 10-methacryloyloxydecyl dihydrogen phosphate; TEGDMA, triethylene glycol dimethacrylate; UDMA, urethane dimethacrylate

Acquisition and processing of digital images

Digital images of a Frasaco A3 Adult Typodont (Frasaco GmbH, Tettnang, Germany) were acquired using a Medit i700 intraoral scanner (MEDIT Corp., Seoul, Republic of Korea) and processed using the software Medit Link v3.0.6 Build 286, and Medit Scan for Clinics v1.9.6 Revision 268 (MEDIT Corp., Seoul, Republic of Korea) (**Fig. 1**).

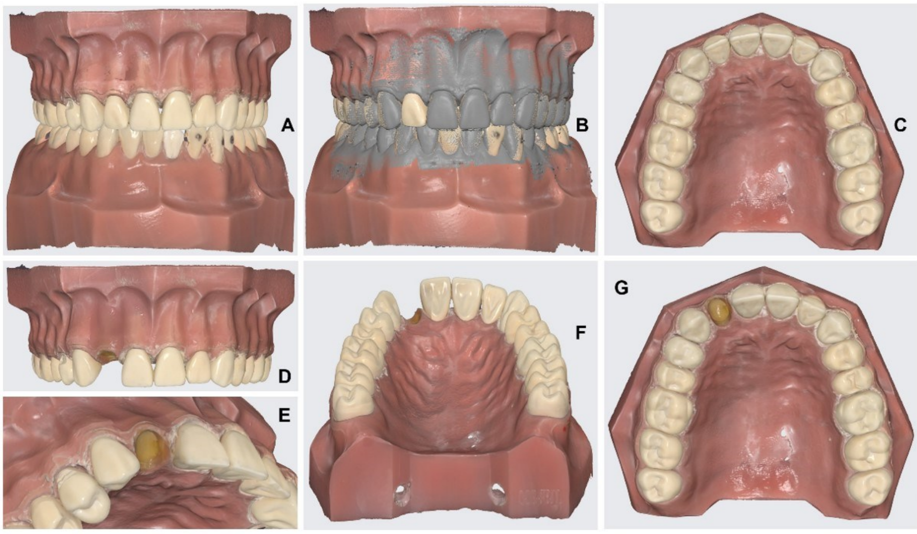

Fig. 1 Images acquired using an intraoral scanner. (A) reference data from both maxillaries in frontal view, (B) occlusion data, (C) reference maxilla in occlusal view, (D) maxilla simulating a lateral incisor agenesis, (E) the same in detail, (F) a view from palatal; (G) maxilla simulating a lateral incisor agenesis in occlusal view

Fig. 2 shows the steps of the digital processing of the data (3Shape CAD/CAM software, Copenhagen, Denmark), focusing on material resistance and occlusal contacts. The connector area was set at 6.6 mm^2, limited by the vestibular, incisal, and gingival parameters. This procedure was repeated according to the manufacturer's instructions for each monolithic CAD/CAM ceramic.

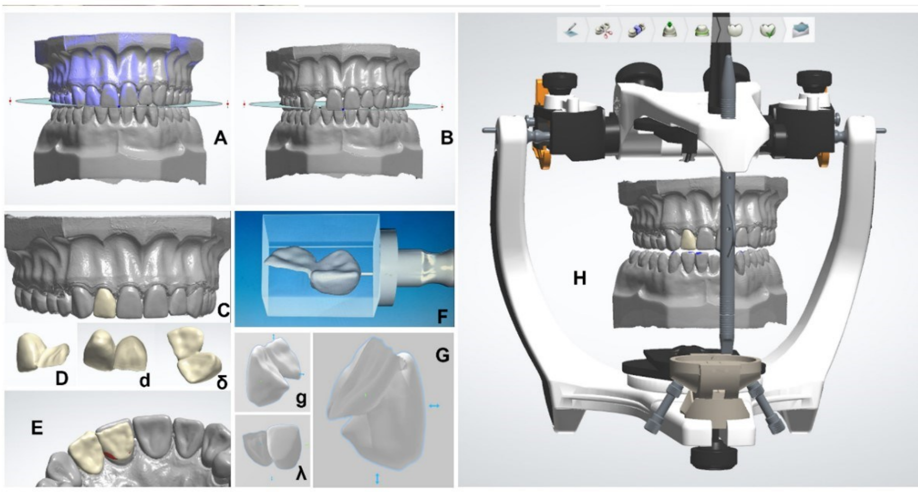

Fig. 2 STL images uploaded to 3Shape software. (A and B) Reference data from both maxillaries in front view (with and without the lateral incisor) for the calibration of the occlusal plane, (C, D, d, δ) details of the planned RBB, (F, G, g, λ) details of the planned RBB to be milled from an ENA block, (H) the digital case mounted in the digital articulator

Single-retainer bridge production

After the design, monolithic RBBs were fabricated using a CAD-CAM inLab milling machine (Dentsply/Sirona, Charlotte, NC, USA), following the manufacturer's laboratory procedures. ABS RBBs were constructed using a Pro2 3D printer (Raise3D, Irvine, CA, USA).

Cementation and testing of resin-bonded bridges

Frasaco right central incisors (Frasaco GmbH, Tettnang, Germany) were used as adherends. As in a clinical context, the superficial glossy surface was removed using a coarse diamond bur simulating the intraoral removal of the aprismatic or fluoridated enamel, followed by surface conditioning for 60 s with 5% hydrofluoric acid. The prepared teeth were shuffled to ensure randomization and operator blinding. A 20-s oil-free air/water spray removed the debris. **Table 2** lists the adhesive protocols used for each type of material. Rely X Ultimate cement was applied using a 3-step adhesive strategy and allowed to self-cure for 7 min after 5 s of photoinitiation (Elipar S10 curing unit, 1200 mW/cm2; 3M ESPE) through the palatal and buccal sides of the Frasaco tooth. All the steps were performed by the same restorative dentist (single operator) with > 30 years of clinical experience. **Fig. 3** shows the details of the shear-bond test settings.

Table 2 Materials used for adherends' surface treatment and adhesion

CEMENT	SUBSTRATE	SURFACE TREATMENT (Frasaco tooth)	SURFACE TREATMENT (RBB)	ADHESIVE SYSTEM
Rely X Ultimate	ABS	5% Hydrofluoric acid	Heliobond	Scotchbond Universal
	ENAMIC	5% Hydrofluoric acid	9.6% Hydrofluoric acid 60 s	
	SUPRINITY	5% Hydrofluoric acid	9.6% Hydrofluoric acid 20 s	
	Y-ZPT	5% Hydrofluoric acid	Al_2O_3 sandblasting	

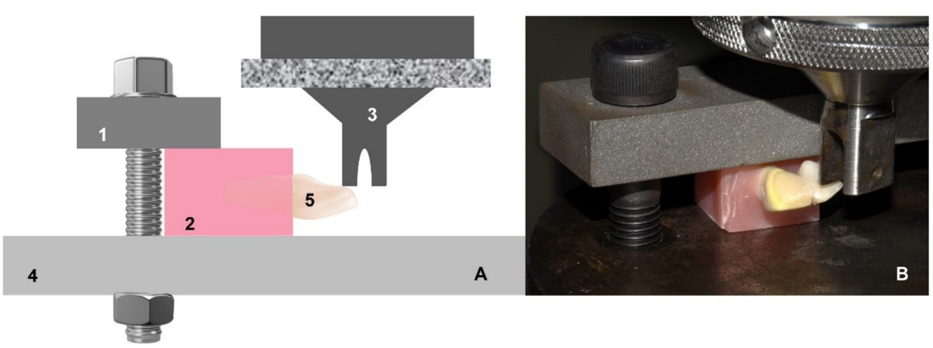

Fig. 3 Scheme of the components designed for testing (A) (1, block stabilizer; 2, base adherend incorporated in acrylic resin block; 3, load cell and piston; 4, stationary base; 5, RBB to be tested); photograph of the shear bonding test (B) with block stabilized on the stationary base and RBB tooth positioned for SBS with the piston positioned 2 mm away from the incisal border

Data analysis

The load to fracture (N) and mean shear stress (MPa) with standard deviations (SD) were registered for each group and compared using boxplot graphics. One-way ANOVA followed by the Tukey-Kramer post-hoc test was used to compare the differences (α = 0.05). A meta-analysis focusing on CAD/CAM materials evaluated the magnitude of the difference between groups based on differences in means and effect sizes (α = 0.05; 95% CI; Z-value = 1.96) using a software program (Stata v18.0; StataCorp, USA). The failure mode was determined by microscopic observation and correlated with the maximum load to fracture of the specimen.

Results

The mechanical behavior, shear bond strength, and failure mode results are shown in **Fig. 4A** and **Table 3**. Despite having a lower performance, the ABS was more consistent, and observing the curve during loading suggested a marked plastic deformation before failure. Box plots in **Fig. 4B** allows rapid visualization of the different mechanical performance between materials. The compared mean ± standard deviation values for the adhesive strength were ENA (24.24 ± 9.05 MPa) < ABS (24.01 ± 1.94 MPa) < SUP (29.17 ± 4.78 MPa) < Y-ZPT (37.43 ± 12.20 MPa).

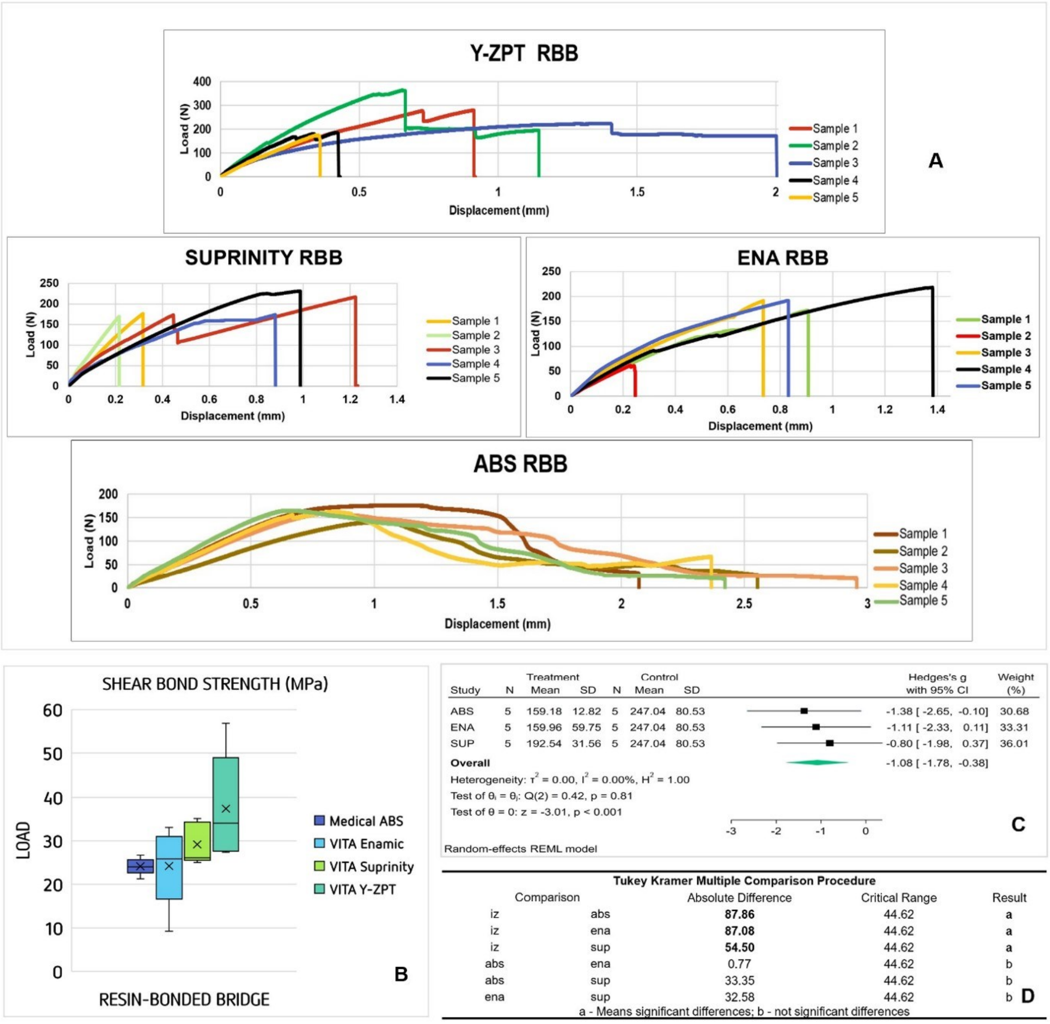

Fig. 4 Specimens behavior under load, from control group (Y-ZPT), Suprinity, Enamic, and ABS groups (A), box plots of shear strength (MPa) of RBBs by type of material (B), forest plot summarizing the effect size of the CAD/CAM materials (C), and comparative procedure between groups after ANOVA (D)

Fig. 4C shows that the mechanical performance of Y-ZPT was significantly better than that of the others (p < 0.001). **Fig. 4D** shows the results of the compared differences (α = 0.05), highlighting the superior shear strength of Y-ZPT, particularly with ENA and ABS.

The failure modes were mainly adhesive for Y-ZPT, cohesive in the RBB for SUP and ENA, and cohesive with plastic deformation of the RBB for ABS (**Fig.5** and **6**, and **Table 3**).

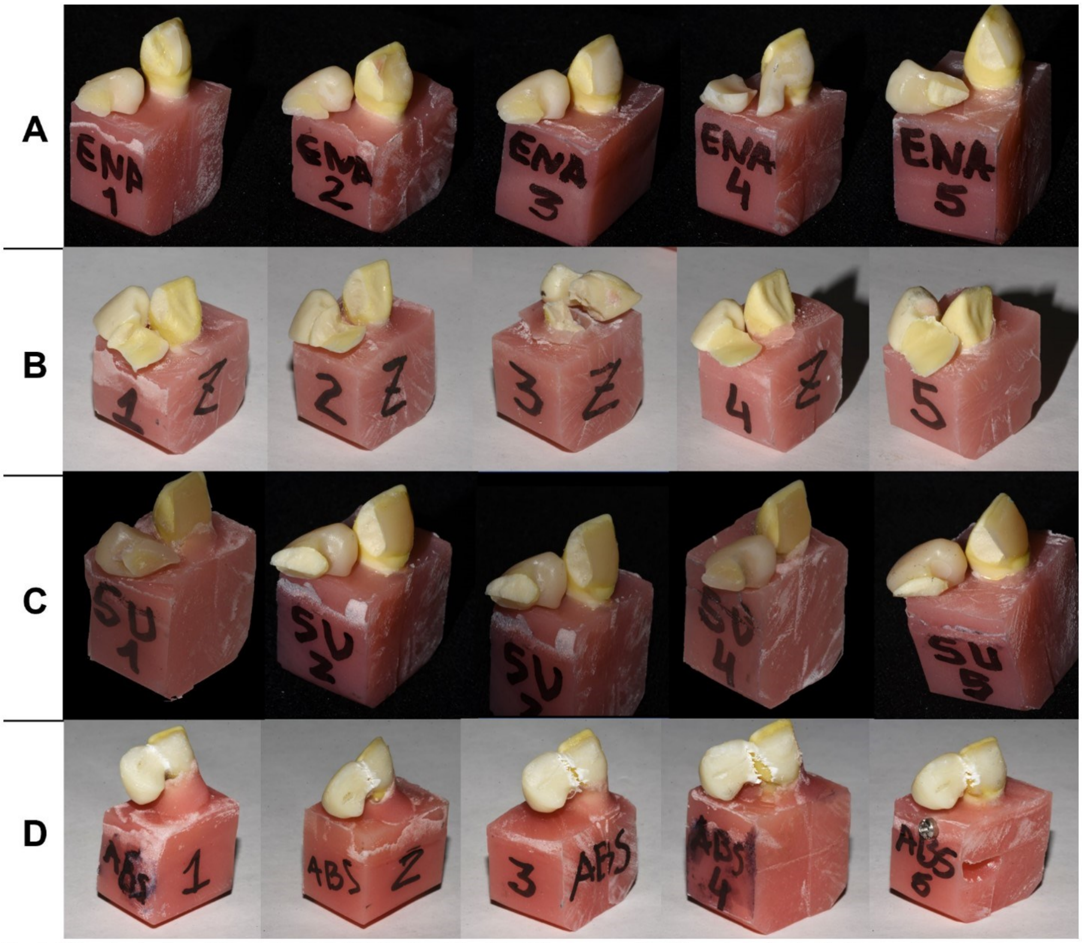

Fig. 5 RBBs after testing. (A) Enamic, (B) Y-ZPT, (C) Suprinity, (D) ABS groups, with different mechanical behavior after shear load

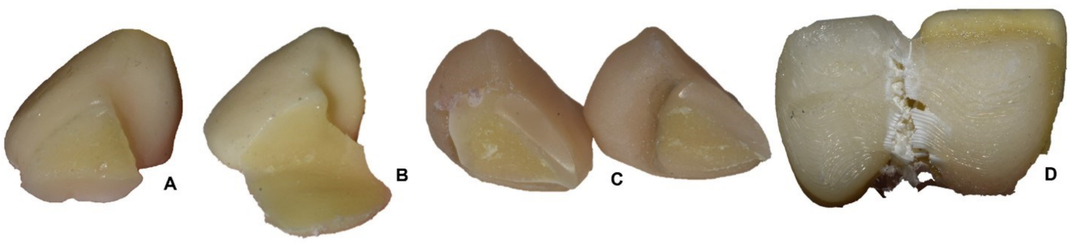

Fig. 6 Details of fractured RBBs and more frequent failure modes by material type. (A) ENA, adhesive interproximal and cohesive in retainer; (B) Y-ZPT, adhesive, with RBB integrity; (C) SUP, cohesive in Frasaco tooth and retainer; (D) ABS, adhesive in interproximal, cohesive with plastic deformation in RBB (no RBBs' tooth loss occurred)

Table 3 Compression strength and mode of failure by group and sample

Groups		**Compression Strength**			**Mode of Failure**		
		N	**MPa**	**Sample**	**AD**	**C_A**	**C_RBB**
Rely X Ultimate	**Medical ABS**	158.45	24.01	1	x		x
	Medical ABS	176.22	26.70	2	x		x
	Medical ABS	140.36	21.27	3	x		x
	Medical ABS	158.28	23.98	4	x		x
	Medical ABS	162.60	24.64	5	x		x
	Failure load		**Shear Strength**				
	Mean (N)	**SD (N)**	**Mean (MPa)**	**SD (MPa)**			
	159.18	**12.82**	**24.12**	**1.94**			
					AD	**C_A**	**C_RBB**
	Vita Enamic	170.52	25.84	1	x		x
	Vita Enamic	61.09	9.26	2	x		x
	Vita Enamic	158.45	24.01	3		x	x
	Vita Enamic	191.42	29.00	4			x
	Vita Enamic	218.30	33.08	5		x	x
	Failure load		**Shear Strength**				
	Mean (N)	**SD (N)**	**Mean (MPa)**	**SD (MPa)**			
	159.96	**59.75**	**24.24**	**9.05**			
					AD	**C_A**	**C_RBB**
	Vita Suprinity	171.75	26.02	1	x		x
	Vita Suprinity	172.16	26.08	2		x	x
	Vita Suprinity	221.43	33.55	3		x	x
	Vita Suprinity	165.31	25.05	4	x		x
	Vita Suprinity	232.03	35.15	5		x	x
	Failure load		**Shear Strength**				
	Mean (N)	**SD (N)**	**Mean (MPa)**	**SD (MPa)**			
	192.54	**31.56**	**29.17**	**4.78**			
					AD	**C_A**	**C_RBB**
	Vita Y-ZPT	271.40	41.12	1	x	x	
	Vita Y-ZPT	375.01	56.82	2	x	x	
	Vita Y-ZPT	224.90	34.08	3	FTF	FTF	
	Vita Y-ZPT	180.4	27.33	4	x		
	Vita Y-ZPT	183.49	27.80	5	x		
	Failure load		**Shear Strength**				
	Mean (N)	**SD (N)**	**Mean (MPa)**	**SD (MPa)**			
	247.04	**80.53**	**37.43**	**12.20**			

AD, adhesive failure; C_A, adherend cohesive failure; C_RBB, bridge cohesive failure; FTF_ Frasaco tooth fracture; MPa, megapascals; N, newton; SD, standard deviation

Discussion

The null hypothesis that no differences would be found in the shear bond strengths among the tested materials in the tested RBB model was rejected, because significant differences existed ($p < 0.01$). The Y-ZPT (control) was the most rigid material in this experimental model, which is consistent with the literature. The ABS, ENA, and SUP groups exhibited consistent mechanical performances.

When speaking about the longevity of rehabilitative treatment, one implicitly thinks of definitive rehabilitation. However, when treating a case of MLIA, rehabilitation must often be temporary and adaptable. This is the case of orthodontic space opening, in which success is reflected in the progressive diastema between the central incisor and the canine tooth. In these specific cases, zirconia RBB is unthinkable because it is too resistant to be removed repeatedly without damaging the supporting tooth and has a laborious adhesive technique that hinders the addition of resin-matrix-based materials. Thus, the possibility of fabricating RBBs with materials that are easier to handle, can be replaced at low cost, or are easier to remove from the supporting tooth, led us to look for alternatives, mainly focusing on managing orthodontic treatments using aligners.

Regarding CAD/CAM materials, the mechanical behavior of RBBs is dependent on the type of material. Transposing the findings to a clinical situation, it can be suggested that using an RBB made of ENA or SUP as their mode of failure led to the complete loss of the pontic, the removal of the retainer, and the manufacture of a new restoration would be necessary. In the case of Y-ZPT, loss of adhesion without RBB structural changes would allow for an immediate new adhesive procedure. As for the ABS RBB, its plastic deformation would allow the patient to have an appointment with his dentist before the pontic is lost, avoiding being toothless.

Despite the expected low shear strength of FRASACO teeth based on a preliminary study, their resistance was sufficient to demonstrate differences in the mechanical behavior of the RBBs, as exclusive adhesive failure was verified only for RBBs manufactured with zirconia, a material with high toughness. Using FRASACO teeth as adherends was very useful because they have a standardized composition and anatomy, allowing the elimination of bias originating from biological factors or different macroanatomies of the palatal face of a natural incisor, which can occur if natural teeth have been used, as only slight asperization was intended, as in a minimally invasive approach. A practical comparison between the materials used to manufacture single-retainer RBBs without inherent ethical restrictions was also possible.

Concerning Medical ABS, it must be highlighted that if manufactured by fused deposition, the orientation of the appendages influences its mechanical characteristics; therefore, a careful design contemplating this aspect is necessary for an excellent final mechanical performance.[36] Complex geometries with a high concentration of stress should be avoided. However, if not possible, fabric from powder should be preferred because the unused powder fills the gaps between the filaments.[29] Nothing was found in the literature about the adhesive protocol for Medical ABS. Considering the chemical composition and ease of handling of the material, an old and well-known hydrophobic resin (Heliobond, Ivoclar Vivadent AG, Liechtenstein) was selected to simplify the adhesive protocol.

One cannot propose RBB as an option to rehabilitate the space of the MLIA without reflecting on occlusal function. Scientific literature focusing on occlusal efforts at the anterior level of the maxilla was not found, leading to a more embracing discussion. A study focusing on the maximum bite force (MBF) refers to a value of approximately 80 N (20% higher in bruxists) in individuals aged–22-48.[37] It varies with malocclusion, sex (higher in males), and age (increase until young adult age), decreasing significantly with vertical and transverse craniofacial and dental discrepancies, and with old age.[38,39] Patients with normal sagittal occlusion are expected to have more molar bite force than patients with malocclusions, with a magnitude 2 to 3 times greater in the molar region than in the anterior region.[40] A recent systematic analysis showed that MBF ranged from 246.22–489.35 N and 5.69–16.1 kg in children and adolescents, respectively,[41] If a contact area of 1 mm^2 is assumed, respective values of 246-489 MPa and 56-158196 would be obtained. However, if the results from T-scan measurements of the occlusal contact area in MBF[42] are considered, revealing a mean value of 155 mm^2 for healthy young adults, the conversion would be to 0.3-3 MPa by mm^2 of contact area.

Reflecting on patients treated for MLIA with space opening must be made because occlusal loads are higher than expected for the average patient whenever hypo-divergence is present.[43] However, at the end of orthodontic treatment, an equilibrated occlusal function is mandatory, with a dispersed distribution of occlusal forces, thus theoretically reducing the adhesive stress on RBBs in the anterior maxilla.

Extrapolating the results of this study to clinical situations, Y-ZPT RBBs are the most suitable for MLIA rehabilitation, which is consistent with the literature. However, more research is needed for newer zirconias with higher yttria contents because of their reduced toughness by almost half. Not testing them, instead of the tougher third-generation, is a limitation of this study. Whenever the option is short-term interim rehabilitation (orthodontic appliance removal or adaptation, periodontal remodeling or maturation, a short period between the end of orthodontic treatment and implant-supported crown placement, or even during the time of osseointegration of the implant), any other material is feasible and preferable because of more straightforward adhesive protocols and removal, if desired.

Printed ABS RBB is the most exciting material. It can be fabricated quickly on the chairside at a very low cost and requires only a hydrophobic resin for surface treatment. Further research using this or similar materials should be conducted in the future.

This study used a specific RBB design, with a retainer on the palatal side of the central incisor. This design could raise constraints in cases of minimal interocclusal space available owing to sagittal or vertical discrepancies that may coexist in MLIA cases. Alternative approaches, such as employing a single retainer adhered to the buccal side of the central incisor or canine tooth, should be equated because of the thin dimensions of the retainer which would not invade the buccal profile of the supporting tooth and a more straightforward cementation technique than the palatal one.

Conclusions

Resin-bonded bridges made of Vita Enamic, Suprinity, Y-ZPT zirconia, or 3D printed ABS can support physiological occlusal loads of the anterior maxilla. They can be used to rehabilitate MLIA in clinical situations. For definitive rehabilitation, Y-ZPT is preferable. Medical ABS, ENA, and SUP are more suitable interim RBB. The option for each material is conditioned by the previous estimation of the time of use and the necessity of removal for orthodontic or surgical techniques.

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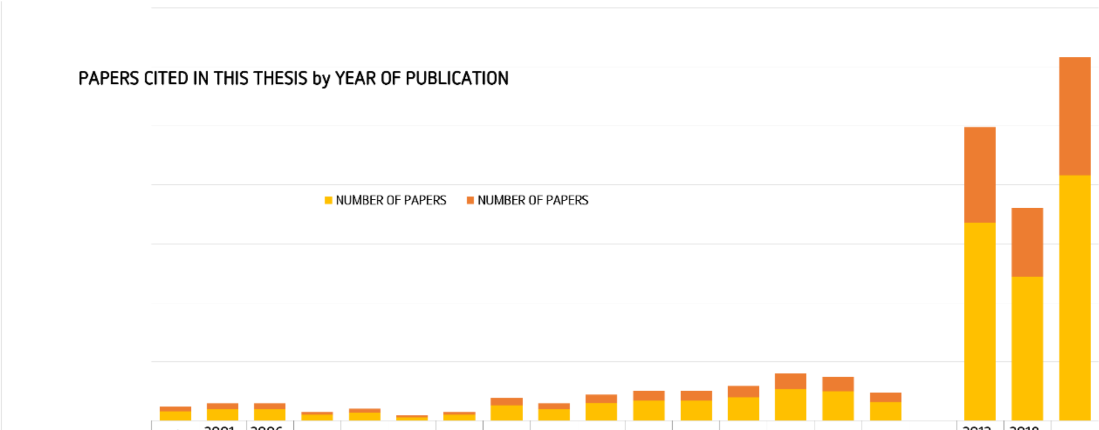
APPENDIX H - Graphical representation of references by the year of the publication



	≤ 2000	2001-2005	2006-2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2013-2023	2018-2023	TOTAL
NUMBER OF PAPERS	3.8	4.8	4.8	2.4	3.4	1.4	2.4	6.3	4.8	7.2	8.2	8.2	9.6	13.0	12.0	7.7	80.8	58.7	100.0
NUMBER OF PAPERS	8	10	10	5	7	3	5	13	10	15	17	17	20	27	25	16	168	122	208

Year of Publication

Figure 61 - Papers cited in this thesis by year of publication

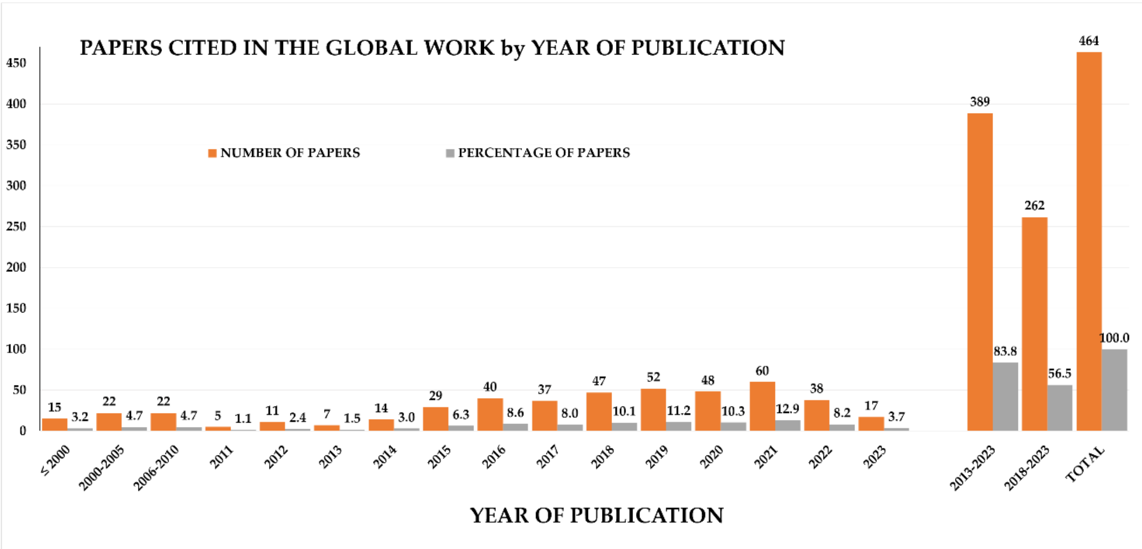


Figure 62 – Number of papers used in the global work, distributed by percentage and year of publication in a total pool of 471 references

MARIA JOÃO CALHEIROS LOBO

De:	Maria João A O Calheiros-Lobo <mjoao.lobo@iucs.cespu.pt>
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1

APPENDIX J - Global list of references numbered by alphabetic order

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