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Effectivness of non-surgical and surgical periodontal therapy in lowering HbA1c in diabetic patients-an integrative review

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Fabio Aspesi

Dissertação conducente ao Grau de Mestre em Medicina Dentária (Ciclo Integrado)

Gandra, 28 de maio de 2021

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Trabalho realizado sob a Orientação de Prof. Dra. Marta Relvas

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Declaration of Integrity

I, as identified above, declare to have acted with absolute integrity in the preparation of this work, confirming that in all the work leading to its preparation I have not resorted to any form of falsification of results or the practice of plagiarism (act by which an individual, even by omission, assumes authorship of the intellectual work belonging to another, in its entirety or in parts of it). Furthermore, I declare that all the sentences that I have taken from previous works belonging to other authors have been referenced or re-written with new words, in which case I have included the citation of the bibliographic source.

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Aspesi F., Relvas M.

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RESUMO

A diabetes é uma doença pandémica global, uma desordem metabólica de etiologia múltipla que se caracteriza por hiperglicemia crónica resultante de defeitos na secreção de insulina, da ação da insulina, ou ambos. A periodontite é uma doença inflamatória crónica iniciada pela acumulação de biofilme de placa bacteriana, dentro da qual a disbiose microbiana conduz a uma resposta inflamatória crónica, não-resolutiva e destrutiva. Nas últimas décadas, muitos estudos investigaram o impacto do tratamento periodontal no controlo glicémico em pessoas com diabetes. O objetivo desta dissertação é fazer uma revisão integrativa para compreender a associação entre a terapia periodontal e os valores da hemoglobina glicosilada (HbA1c). Foi realizada uma pesquisa em PUBMED e dos 277 artigos encontrados, apenas 21 foram considerados por serem mais relevantes. Como foi reconhecido durante algum tempo, os resultados mostram uma correlação entre as duas doenças e a sua ligação reside no processo inflamatório. No paciente diabético, isto resulta em valores de HbA1c mais elevados e numa situação difícil de controlar. Ser capaz de controlar o estado inflamatório do periodonto através de protocolos de higiene oral e terapia periodontal tem vários benefícios num quadro clínico complicado em situações de controlo glicémico deficiente. A terapia periodontal não cirúrgica revela-se eficaz na redução significativa dos níveis de HbA1c em doentes diabéticos.

Palavras-chave: “Periodontal disease”; “Glycated hemoglobin A”; “periodontitis”.

ABSTRACT

Diabetes is global pandemic disease, a metabolic disorder of multiple aetiology that is characterised by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Periodontitis is a chronic inflammatory disease that is initiated by the accumulation of dental plaque biofilm, within which microbial dysbiosis leads to a chronic, non-resolving and destructive inflammatory response. In the last decades, many studies investigated the impact of periodontal treatment on glycemic control in people with diabetes. The aim of this dissertation is to conduct a review of the published literature to understand the association between periodontal therapy and glycated haemoglobin (HbA1c) values. A search was conducted in PUBMED and of the 277 articles found, only 21 were considered for being more relevant. As has been recognised for some time, the results show a correlation between the two diseases and their link lies in the inflammatory process. In the diabetic patient, this results in higher HbA1c values and a situation that is difficult to control. Being able to control the inflammatory state of the periodontium through oral hygiene protocols and periodontal therapy has several benefits in a complicated clinical picture in situations of poor glycaemic control. Non-surgical periodontal therapy proves effective in significantly lowering HbA1c levels in diabetic patients.

Key-words: “Periodontal disease”; “Glycated hemoglobin A”; “periodontitis”.

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ABREVATIONS

WHO-World Health Organization

HbA1c-glycated haemoglobin A

LPS-lipopolysaccharides

TNF-α- tumor necrosis factor–α

IL-6-interleukin-6

IL-1β-interleukin-1β

IF- γ-interferon gamma

CRP- C-reactive protein

SRP-scaling and root planning

DM-diabetes mellitus

T1DM-diabetes mellitus type 1

T2DM-diabetes mellitus type 2

AGEs-advanced glycation end-products

I. INTRODUCTION

Noncommunicable diseases now make up 7 of the world's top 10 causes of death, according to WHO (World Health Organization)'s 2019 Global Health Estimates, published. This is an increase from 4 of the 10 leading causes in 2000. The estimates clearly highlight the need for an intensified global focus on preventing and treating cardiovascular diseases, cancer, diabetes and chronic respiratory diseases, as well as tackling injuries, in all regions of the world. It is estimated there are already 415 million adults ages 20-79 with diabetes, including 193 million undiagnosed. In the Eastern Mediterranean, deaths from diabetes have more than doubled and represent the greatest percentage increase of all WHO regions (1,2).

Diabetes is global pandemic disease, a metabolic disorder of multiple aetiology that is characterised by chronic hyperglycemia (elevated blood glucose levels) with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (2,3).

Hyperglycemia leads to development of the complications associated with diabetes that arise from long-term damage, dysfunction and failure of various organs and body systems that impact on wellbeing and quality of life. A diagnosis of diabetes can be made following a random venous plasma glucose test, a fasting plasma glucose test, a two-hour plasma glucose tolerance test following 75 g oral glucose, or a non-fasting glycated haemoglobin (HbA1c) measurement (4).

Type 1 and type 2 are the principal categories of diabetes. Type 1 diabetes results from insulin deficiency due to autoimmune destruction of the β-cells of the islets of Langerhans in the pancreas. Insulin deficiency leads to an inability to control blood glucose levels, and hyperglycemia develops. Type 2 diabetes accounts for around 90% of cases of diabetes, and is caused by impaired insulin secretion and increased insulin resistance (4).

The objective of diabetes treatment is to reduce the risk of microvascular and macrovascular complications by controlling blood glucose, with maintenance of HbA1c below a target value. HbA1c values <53 mmol/mol (<7.0%) would usually indicate good control. In a non- diabetic person, HbA1c is typically around 37 mmol/mol (5.5%).

Reductions in HbA1c are highly relevant, because it has been shown that each 1% reduction in HbA1c (approximately 11 mmol/mol) is associated with measurable reductions in diabetes complications (5).

Periodontitis is a chronic inflammatory disease that is initiated by the accumulation of dental plaque biofilm, within which microbial dysbiosis leads to a chronic, non-resolving and destructive inflammatory response. Treatment of periodontitis involves professional care to reduce the bacterial challenge, together with patient education, motivation, and empowerment to optimize oral hygiene and reduce or eliminate risk factors such as smoking (4).

Periodontal treatment (professionally delivered root surface debridement and optimized oral hygiene) reduces the bacterial load in the subgingival environment, and this, in turn, results in reduced periodontal inflammation. The reduction of the subgingival bacterial load also leads to reduced levels of circulating bacteria and bacterial products (6).

The precise mechanisms that lead to reductions in HbA1c and improved glycemic control following periodontal treatment in people with diabetes are not completely clear but are presumed to arise from the combined effects of reduced systemic inflammation and reduced bacterial challenge that may have an impact on resistance and signaling of insulin and, consequently, on glycemic control (7,8).

Many studies have been conducted over the last 2–3 decades that investigated the impact of periodontal treatment on glycemic control in people with diabetes. The findings of these studies have generally been consistent in reporting reductions in HbA1c following periodontal therapy (9).

II. OBJECTIVE

The goal of this work is to do an integrative review about the effectiveness of non-surgical and surgical periodontal therapy in lowering HbA1c levels in diabetic patients.

III. METHODS

PICO model was used: Patient (with diabetes), Intervention (with periodontitis), Control (patient without diabetes) and Outcome (association of periodontal treatment in patients with diabetes). The built question is the follow: is periodontal treatment effective in controlling HbA1c levels? Methods has been inspired from PRISMA protocol by its use of a flow diagram.

1. Research methodology

A bibliographic search was performed on electronic platform via PUBMED. Different combinations of Keys words were used: “Periodontal disease” AND “Glycated hemoglobin A” OR “periodontitis”.

2. Eligibility criteria

Several kinds of publication were taken in consideration: randomized clinical trial, randomized control clinical trial, pilot study, meta-analysis and systematic review. Only articles dealing with periodontal treatment in association with diabetes and published, de January 2012 until december of 2020, in english were selected. Only the ones published in full and in electronical form were elected. Title, resume and abstract were analyzed in order to assess relevance of each articles. Then potentially eligible articles were examined by a full text analyzing to check utility for our study.
Inclusion and exclusion criteria were the following:

- Studies explaining association of periodontitis and diabetes were included
- Studies describing influence of periodontal treatment on glycated hemoglobin A were included
- Articles not written in english, before 2011 were excluded
- Literature reviews were excluded for results

3. Screening methodology

After identification of eligibly articles through several databases and platforms, selection of relevant articles was performed in order to investigate the correlation between periodontitis and diabetes.

Total of articles found was compiled in Mendeley citation manager, where duplicates were removes. Evaluation of each publication in its entirety was realized to elect accurate publication which will meet the purpose of the study. Screening included analyze of title and abstract in order to remove non-relevant article for this review. After screening phase, all articles were read in full-length, to assess eligibility for qualitative analysis. Different factors were chosen to evaluate articles selected: name, authors, years, type of study, sample size, part tested, technic used, result and conclusion.

Elected articles needed to respond to the outcome of this study which is effectiveness of periodontal therapy on glycated hemoglobin A.

IV. RESULTS

A total of 277 articles were identified on PubMed database, between 2012 and 2020. With application of study eligibility criteria (studies about effectiveness of periodontal therapy on glycated hemoglobin A), 93 articles were taken into consideration. After screening and application of inclusion and exclusion criteria, 30 articles were included for qualitative analysis. Of these, 19 articles were selected that assess HbA1c levels before and after periodontal therapy; the other studies identified but not selected were used later to deepen and extend knowledge on this review subject matter and enrich discussion. All the procedure is explained in flow chart procedure (Figure 1).

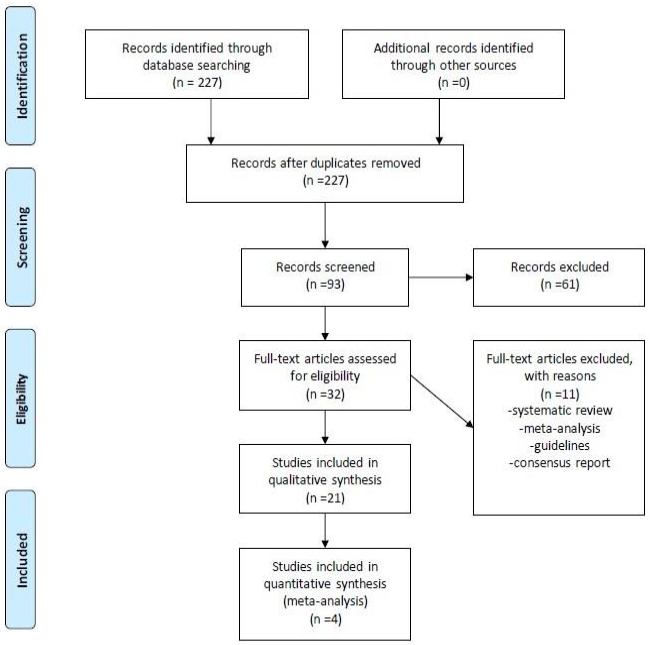

Figure 1

Extracted data were compiled in table 1: authors, year country sample size results and conclusion.

Table 1: Relevant data gathered from the selected studies

Authors [YEARS]	Country	Sample size	Results	Conclusion
Chen L *et al.* [2012] (10)	China	45 treatment group 145 treatment group 244 control group	Declined significantly in treatment group 2 (P<0.05), the intergroup difference for HbA1c, FPG, TNF-a, and lipid profiles was not statistically significant after therapy (P>0.05).	Non-surgical periodontal treatment can effectively improve periodontal and circulating inflammatory status. Despite a lack of strong evidence, trends in some results support improved glycemic control after periodontal treatment in patients with diabetes

Moeintaghavi A *et al*. [2012] (11)	Australia	22 treatment group 18 control group	From baseline to follow-up (after three months), HbA1c levels decreased in the treated group (p = 0.003). In the same time period, FPG, GI, PPD and CAL increased in the control group (p = 0.016,0.0, 0.0 and 0.004, respectively) but HbA1c did not change significantly.	Non-surgical periodontal therapy could improve metabolic control in diabetic patients
Mendoça A *et al.* [2012] (12)	Brasil	61 patients with periodontitis and DMT2 (21 quadrant with treatment and 21 without treatment)	Pocket dept and clinical attachment level (CAL) of root planning improved significantly after therapies (p<0.05), without differences between groups at any time-point (p>0.05)	Surgical debridement and non-surgical debridement associated with systemic antimicrobials did not differ in terms of clinical benefits for RP in diabetics up to 6 months post-therapies. RP treated by SD presented increased levels of cytokines.
Cirano F *et al*. [2012] (13)	Germany	16 patients with periodontitis and DMT2 15 without DMT2	Diabetic subjects treated with full mouth ultrasonic debridement had a clinical response like that of non-diabetic subjects at all pocket depths. No adverse effects or medical disturbances were observed in either group during treatment. FPG and HbA1c levels remained unaltered after treatment.	Within the limitations of this study, FMUD promoted clinical improvements in patients with type 2 uncontrolled diabetes and generalized severe periodontitis.
Engebreston S *et al.* [2013] (14)	USA	257 treatment group 257 control group	At 6 months, mean HbA1c levels in the periodontal therapy group increased 0.17% (SD, 1.0), compared with 0.11% (SD, 1.0) in the control group	Non-surgical periodontal therapy did not improve glycemic control in patients with type 2 diabetes and moderate to advanced periodontitis.
Engebretson S *et al*. [2013] (15)	USA	300 treatment group 300 control group	The primary outcome was change in HbA1cfrom baseline to 6 months and the trial was powered to detect a between-group difference of 0.6%. Secondary outcomes included changes in periodontal clinical measures, fasting plasma glucose, the Homeostasis Model Assessment (HOMA2) and the need for rescue diabetes or periodontal therapy	Dental and medical researchers monitor participants with two chronic diseases to determine if treatment of one condition affects the status of the other.
Perayil J *et al*. [2014] (16)	India	30 patients with periodontitis and DMT2 30 without periodontitis	There were significant differences between Group A and Group B regarding baseline levels of OHI-S, GI, PPD, and HbA1c (p<0.05). At the end of three months, Group B showed improvement in all clinical parameters(p<0.05), and their HbA1c levels also significantly decreased (p<0.05)	The HbA1c levels of non-diabetic subjects with periodontitis (Group B) was significantly reduced three months after non-surgical periodontal therapy, although they never reached the same level as that of the non-diabetic subjects without periodontitis
Gay I *et al*. [2014] (17)	USA	66 treatment group 60 control group	Baseline mean SD HbA1c for the test and control groups were 9.02.3% and 8.42.0% respectively. Non-significant difference in HbA1c reductions (0.62.1% and 0.31.7%) was found between test and control groups at 4 months.	No statistically significant differences were found in the changes of HbA1c levels between test and control groups. Non-surgical periodontal therapy improved the magnitude of change in periodontal parameters as compared to the control subjects.

Schjetlein A *et al*. [2014] (18)	Greenland	62 patients with periodontitis and DMT2	The prevalence of periodontitis decreased significantly from 21.0 to 0% (Pb0.001) after 3 dental examinations. No change in HbA1Clevelswas observed (p-0.440).	Dental health status based on Periodontal Screening Index (PSI) and bleeding on probing (BOP) seemed to improve after dental health care indicating a need for increased awareness among patients and health care professionals. HbA1C levels were not improved among the patients.
Koromantzos P *et al*. [2014] (19)	Mexico	77 treatment group 77 control group	Baseline mean HbA1c was 9.0 (2.3%) and 8.4 (2.0%) for the experimental and control groups, respectively. Four months after baseline, HbA1c decreased by 0.6% (8.4 [1.9%]) in the experimental group, and by 0.3% (8.1 [1.8%]) in the control group. The difference between groups was not statistically significant (p= 0.89). Linear regression analyses demonstrated a correlation between change in HbA1c levels and baseline HbA1c.	Non-surgical periodontal therapy has no statistically significant impact on HbA1c levels of Mexican American patients with DM type 2 and periodontal disease.
Mirnić J *et al*. [2014] (20)	Serbia	41 treatmen group 21 control group	Using a combination of metronidazole and amoxicillin significantly improved the metabolic outcome in addition to periodontal health in diabetic subjects with periodontitis.	The non-surgical periodontal treatment using a combination of metronidazole and amoxicillin significantly improved the metabolic outcome in diabetic subjects with periodontitis.
Raman R *et al*. [2014] (21)	Malesya	20 treatment group 20 control group	HbA1c levels in both groups recording have statistically significant reduction (p = 0.038). Participants who demonstrated≥50% reduction in PPD showed significant reductions of HbA1c and hs-CRP levels (p = 0.004 and p = 0.012).	Both NSPT and OHI demonstrated improvements in other clinical parameters as well as HbA1c and CRP levels.
Palka K *et al.* [2015] (22)	India	50 treatment group 50 control group	In patients receiving treatment, periodontal parameters significantly improved and HbA1c decreased by 10.8%.	Nonsurgical periodontal therapy improved glycemic control and periodontal health in patients with type 2 diabetes.
Alshehri M *et al*. [2017] (23)	Saudi Arabia	30 treatmetn group 30 control group	After 90 days of follow-up, there was a significant reduction in the severity of periodontal parameters in patients in Group 1 compared with Group 2. After 90 days of follow-up, there was also a significant reduction in HbA1c among patients in Group 1 compared with Group 2.	Scaling and root planing with adjunct use of an essential oil-based oral rinse is more effective in the treatment of periodontal inflammation in T2D patients than SRP alone. This approach also helps reduce hyperglycemia in T2DM patients as compared with when SRP is performed alone.
Mauri-Obradors E *et al.* [2017] (24)	Spain	45 treatment group 45 control group	Treatment significantly improved the periodontal and metabolic parameters (p<0.05) whereas in the control group no improvement was observed. These results were consistent with the bacteriological results in most but not all cases.	Non-surgical periodontal treatment resulted in a better glycemic status of type 2 diabetes patients and demonstrated the importance of oral health in their general health.
Wang S *et al*. [2017] (25)	China	22 treatment group 22 control group	The probing depth (PD) and attachment loss (AL) were significantly improved, the serum levels of TNF-α and IL-6 were significantly decreased, and APN and FGF-21 exhibited substantial increases in the intervention group after 3	Periodontal treatment may relieve periodontal inflammation, which causes a reduction of insulin antagonizing adipokines and an increase in insulin sensitizing adipokines, thereby eliciting an

			months. The glycated hemoglobin (HbA1c) levels decreased after 3 months compared with baseline ($p < 0.05$), but the intervention group exhibited a significantly greater change ($p < 0.05$).	improvement in glycemic control
Hayashi J *et al*. [2017] (26)	Japan	12 patients with periodontitis and DMT2	After the periodontal treatment, the glycated hemoglobin value was significantly improved.	Within the limitations of this pilot study, periodontal treatment may be effective not only in improving metabolic control, but also in reducing the risk of diabetic kidney and liver disease in patients with T2DM.
Tsobgny-Tsague N *et al*. [2018] (27)	Camerun	17 treatment group 17 control group	Immediate no-surgical periodontal treatment induced a reduction of HbA1c levels by 3.0 ± 2.4 points from 9.7 ± 1.6% at baseline to 6.7 ± 2.0% 3 months after nonsurgical periodontal treatment ($p<0.001$) but the change was not significant in group2, from mean 8.9 ± 0.9% at baseline vs 8.1 ± 2.6% after 3 months ($p=0.24$).	No-surgical periodontal treatment markedly improved glycemic control with an attributable reduction of 2.2 points of HbA1c in poorly controlled T2D patients.
D'Aiuto F *et al*. [2018] (28)	UK	133 treatment group 131 control group	At baseline, mean HbA1c was 8·1% (SD 1·7) in both groups. After 12 months, unadjusted mean HbA1c was 8·3% (SE 0·2) in the control group and 7·8% (0·2) in the treatment group; with adjustment for baseline HbA1c, age, sex, ethnicity, smoking status, duration of diabetes, and BMI, HbA1cwas 0·6% (95% CI 0·3–0·9; $p<0·0001$) lower in the treatment group than in the control group.	Compared with control periodontal treatment, intensive periodontal treatment reduced HbA1c in patients with type 2 diabetes and moderate-to-severe periodontitis after 12 months. These results suggest that routine oral health assessment and treatment of periodontitis could be important for effective management of type 2 diabetes.
El-Makaky Y *et al*. [2019] (29)	Egypt	88 patients with periodontitis and DMT2 44 control group	Regarding clinical and metabolic parameters at baseline, no statistically significant differences were displayed between the two groups. However, at 3-month follow-up period the patients within the test group demonstrated significantly better clinical and metabolic outcomes than patients in the control group.	The non-surgical periodontal treatment using a combination of metronidazole and amoxicillin significantly improved the metabolic outcome in addition to periodontal health in diabetic subjects with periodontitis.

Table 2 shows the values of Hba1c of diabetic patients treated with periodontal therapy in pre- and post-treatment.

All studies report a statistically significant decrease in Hba1c values between baseline data and the end of periodontal treatments conducted in each study; the analysis of the values reported in the studies examined underlines the fact that the therapies must be conducted for at least three months and if the planning of the therapy is perpetuated over time the values turn out to be lowered in an increasingly considerable and meaningful way.

Table 2: Initial and final HbA1c values

Authors [YEARS]	**Groups**	**Baseline (%HabA1c)**	**End treatment (%HabA1c)**
Chen L *et al*. [2012] (10)	treatment group 1 treatment group 2 control group	7.31±1.23 7.29±1.55 7.25±1.49	7.09±1.34 6.87±1.12 7.38±1.57
Moeintaghavi A *et al*. [2012] (11)	treatment group control group	8.15±1.18 8.72±2.22	7.41±1.18 8.97±1.82
Engebreston *S et al*. [2013] (14)	treatment group control group	7.84±0.65 7.77±060	7.69 7.68
Perayil J *et al*. [2014] (16)	Group A (control group) Group B (treatment group)	5.38±0.22 6.08±0.23	5.31±0.19 5.67±0.33
Gay I *et al*. [2014] (17)	experimental group control group	9.0±2.3 8.4±2.0	8.4±1.9 8.1±1.8
Schjetlein A *et al*. [2014] (18)	treatment group control group	7.3 7.0	7.0 7.0
Koromantzos *et al*. [2014] (19)	treatment group control group	9.0±2.3 8.4±2.0	8.4±1.9 8.1±1.8
Mirnic *et al*. [2014] (20)	treatment group 1 treatment group 2	6.19±0.44 8.5±1.53	*
Raman R *et al*. [2015] (21)	NSPT group OHI group	7.8±1.5 7.6±1.5	7.1±1.2 7.1±1.2
Palka K *et al*. [2015] (22)	treatment group no treatment group	8.17±2.49 7.87±2.56	7.29±1.61 8.06±2.72
Alsheri M *et al*. [2017] (23)	group 1 (periodontal therapy and essential oil)	9.3±0.7 8.7±0.7	6.1±0.7 7.4±0.7

	group 2 (only periodontal therapy)		

Mauri-Obradors E *et al.* [2017] (24)	treatment group control group	7.75 7.67	7.75 7.2
Wang S *et al*. [2017] (25)	treatment group control group	7.63±0.89 7.67±1.33	6.99±0.77 7.41±1.32
Hayashi J *et al*. [2017] (26)	treatment group	7.2±0.6	6.8±0.6
Tsobgny-Rsague N *et al*. [2018] (27)	treatment group control group	9.7±1.6 8.9±09	6.7±2.0 8.1±2.6
D'Aiuto F *et al*. [2018] (28)	intensive therapy control therapy	8.1 8.0	7.8 8.3
El-Makaky Y *et al*. [2019] (29)	treatment group control group	8.12±0.74 8.21±0.71	7.27±0.5 8.34±0.64

* The authors report the results of this study did not absolutely support the assumption that the level of glycemic control significantly affected the periodontal therapy outcome in diabetics.

V. DISCUSSION

1. Periodontitis

Periodontitis is primarily an anaerobic microbial infection that results in loss of connective tissue and bone support that develops from intraoral biofilms harboring periodontal pathogenic microorganisms and is a major cause of tooth loss in adults. Nearly half of the United States population over the age of 30 is estimated to have periodontitis, with 38% having moderate or advanced diseases (14,22,30).

Periodontitis is diagnosed when there is gingival inflammation, connective tissue and alveolar bone loss, and apical migration of junctional epithelium. Clinical signs include increased probing pocket depth or clinical attachment loss; periodontal tissue destruction that is observed in periodontitis is host-mediated through the release of pro-inflammatory cytokines in local tissues by immune cells in response to the bacterial flora and its products/metabolites, especially lipopolysaccharides (LPS) (16,31,32).

In periodontitis, there is an increased production of pro-inflammatory mediators, such as tumor necrosis factor–α (TNF-α), interleukin–6 (IL-6), interleukin–1β (IL-1β), and interferon gamma (IF-γ), and increased levels of acute-phase proteins, such as C-reactive protein (CRP). The systemic inflammation associated with periodontitis has been found to aggravate systemic diseases (31, 33).

The American Academy of Periodontology treatment guidelines stress that periodontal health should be achieved in the least invasive and most cost-effective manner. Treatment of periodontitis involves professional care to reduce the bacterial challenge (oral hygiene instruction, scaling and root planing), together with patient education, motivation and empowerment to optimize oral hygiene, remove plaque, calculus and bacterial toxins from deep periodontal pockets and reduce or eliminate risk factors such as smoking. Adjunctive therapy, such as antimicrobial therapy and host modulation are incorporated into the treatment regimen as required on a case-by-case basis (4,21).

A primary role of scaling and root planing (SRP) is to remove supra- and subgingival dental plaque and calculus. However, the overall effectiveness of SRP is compromised in specific clinical scenarios, such as presence of deep periodontal pockets and/or

furcation areas where complete mechanical removal of plaque and calculus deposits is difficult; therapeutic regimes such as use of antibiotics, oral rinses, and laser therapy and antibiotic therapy as adjunct to conventional SRP have been proposed to eradicate periodontal inflammatory conditions (23).

Periodontitis disproportionally affects different demographic categories of the population with individual suffering from other pathologies more vulnerable. In this scenario, the prevalence of periodontitis in diabetic subjects is estimated to be double or even triple that in the normal population, and a bidirectional relationship appears to exist between the diseases (13).

2. Diabetes

Diabetes mellitus (DM) is a common endocrine/metabolic disorder characterized by alterations in the metabolism of carbohydrates, proteins, and lipids. Chronic hyperglycemia, however, underlies both the incidence and the progression of DM related microvascular complications (retinopathy, nephropathy, neuropathy). DM occurs in two main types: type 1 (T1DM) and type 2 (T2DM). T1DM is associated with pancreatic B cell destruction, is prevalent in children and accounts for 5–10 % of individuals with diabetes. T2DM is associated with a progressive defect in insulin production that is caused by insulin resistance and accounts for 90–95 % of all individuals with DM (22,33,34).

Insulin resistance affected by both T2DM and periodontitis have been associated to chronic state of infection and inflammation. The liberation of lipopolysaccharide and the subsequent release of IL-1β, TNF-α and IL-6 are included as possible mechanisms. Consequently, it has been shown that if the infection and inflammation reduced, this may have a positive impact on glycemic parameters (fasting plasma glucose and glycated hemoglobin (HbA1c); those are some factors that initiate and maintain an inflammatory response and regulate the transcription of human acute phase reactants, like C-reactive protein (CRP). CRP is a sensitive inflammatory marker and an independent predictor of cardiovascular diseases (35,36).

Metabolic dysregulation in diabetes because of prolonged exposure to chronic hyperglycemia can lead to the glycosylation of proteins and lipids, called advanced

glycation end-products (AGEs). They can explain many of the sequelae of diabetes, including microvascular complications (35).

For instance, the poor glycemic control of diabetic patients, defined as glycated hemoglobin (HbA1c) values >7%, is associated with microvascular and macrovascular complications (35).

HbA1c measurements provide an indication of blood glucose levels over the previous three months, as this is the life span of erythrocytes. The measurement of HbA1c is routine in medical practice as part of the long-term evaluation of diabetes control, as it indicates how much hemoglobin in the blood has become glycated (i.e., chemically bonded with glucose). Whereas historically, HbA1c was reported as a percentage (i.e., the percentage of hemoglobin that has been bound by glucose), in recent years, the UK has switched to reporting HbA1c in millimoles per mole (mmol/mol) (for example, HbA1c 7% = 53 mmol/mol, HbA1c 8% = 64 mmol/mol). The diagnostic threshold for diabetes using HbA1c (non-fasting) is 48 mmol/mol (6.5%) (4).

3. Relationship between periodontitis and diabetes

Evidence indicates a “two-way” relationship between T2DM and periodontitis; both are chronic, inflammation driven diseases that often occur in the same individuals and mutually and adversely affect each other. Many epidemiological studies have demonstrated that T2DM may increase the risk of periodontitis by two- to three-fold in especially susceptible individuals (25,37).

Although most of the available evidence tends to suggest that diabetes adversely affects periodontal health, some emerging clues tentatively support adverse effects of periodontitis on diabetes. One potential mechanism for the influence of periodontitis on diabetes status may be that local periodontal infection results in a systemic burden of inflammatory mediators that exacerbate the existing metabolic disorder in patients with diabetes (10).

Studies indicate that the control of chronic inflammatory processes caused by periodontitis may constitute a new approach in reducing the risk of complications in patients with T2DM (figure 2). Clinical trials have been designed to determine the possible beneficial effects of conventional periodontal treatment in diabetic patients,

consisting of the mechanical removal of the subgingival biofilm by means of SRP and have shown that these treatments not only improves periodontal status in patients with type 2 diabetes and periodontitis, but also may help improve glycemic control (35,36).

Chronic hyperglycemia such as occurs in DM has been related to tissue damage because endothelial cells take up glucose passively in an insulin-independent manner. In diabetics, both chronic infection by Gram-negative bacteria and the chronic endotoxemia associated with periodontal disease are thought to induce insulin resistance and worsen glycemic control. Insulin resistance is further exacerbated by inflammatory mediators such as IL-1β, IL-6 and TNF-α, which influence the metabolism of glucose and lipids (34).

Initial periodontal therapy, including scaling and root planing (SRP) alone or in conjunction with adjunctive approaches such as antimicrobials, may improve clinical parameters in non-diabetic and diabetic subjects due to the reduction in pathogens and the establishment of a local microbiota compatible with periodontal health. Periodontal treatment reduces the bacterial load in the subgingival environment, and this, in turn, results in reduced periodontal inflammation (4,12).

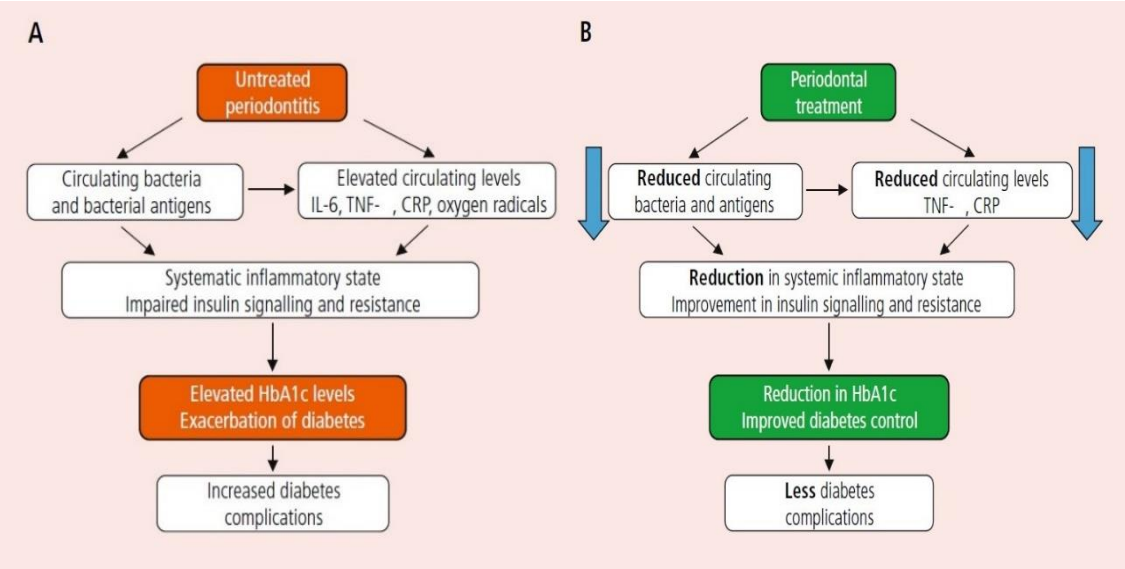

Figure 2: Potential mechanisms linking periodontitis and diabetes, and the impact of periodontal therapy on diabetes control. Adapted with permission from Preshaw PM, Bissett SM. Periodontitis and diabetes. Br Dent J. 2019;227(7):577–84.

A: In untreated periodontitis, bacteria and bacterial antigens together with pro-inflammatory mediators and cytokines enter the circulation and contribute to an upregulated systemic inflammatory state. This results in impaired insulin signalling and increased insulin resistance, leading to elevated HbA1c levels and increased diabetes complications.

B: Following periodontal therapy and reductions in periodontal inflammation, there are reduced levels of circulating bacteria and antigens, and reduced circulating levels of cytokines and inflammatory mediators. This results in a reduction in the systemic inflammatory state, leading to improved insulin signalling and reduced (improved) insulin resistance. In turn, there is a reduction in HbA1c, improved diabetes control and less diabetes complications.

The presence of periodontitis itself in patients with T2DM has been found to influence patient glycemic and metabolic control. This influence is due to local periodontal infection, which result in a systemic load of inflammatory mediators that exacerbate the existing metabolic disorder. In patients with T2DM, studies suggest that reducing periodontal infection and inflammation with periodontal treatment may facilitate metabolic control and improve insulin sensitivity, by reducing peripheral inflammatory cytokine levels (30).

Periodontal therapy and the removal of the cause of this local chronic inflammation may positively influence inflammatory responses and insulin resistance by decreasing and increasing the levels of insulin-sensitizing adipokines, which would then improve glycemic control in these patients; these results support that elimination of periodontal infection can improve glycaemic control because periodontal infection leads to inflammation low-grade inflammation characterized by an up-regulation of pro-inflammatory cytokines (25,27).

The inflamed periodontium produces pro-inflammatory cytokine that can bring about insulin resistance by interfering with glucose and lipid metabolism and lead to decreased insulin production by causing apoptotic cell death of pancreatic β cells**,** thereby leading to a vicious cycle. Thus, by controlling the inflammation through SRP, we can alleviate the exacerbation of insulin resistance and, thus, decrease the systemic level of sugar and the non-enzymatic glycosylation of hemoglobin (16).

The elevated serum level of IL-1β, IL-6 and TNF-α that, associated with periodontitis, antagonize the action of insulin and increase the insulin resistance; re-establishing good periodontal health in type 2 diabetics with periodontal disease has the potential of greatly improving metabolic control and systemic inflammatory challenge, and therefore non-surgical periodontal therapy can significantly reduce the level of HbA1c in T2DM patients with periodontitis (21,29).

Periodontal therapy improves glycaemic control by decreasing pro-inflammatory mediators: an improvement in periodontal parameters and a decrease in HbA1c levels after mechanical periodontal therapy, administered with no changes in medical therapy or diet, in DM2 patients with periodontitis suggest the improvement in the HbA1c values could have been due to reduction in gingival index and bleeding on probing. A decrease

of TNF, HbA1c and periodontal parameters in DM2 patients after periodontal therapy, support for the possibility that periodontal therapy may reduce HbA1c values by reducing TNF concentrations in DM2 patients with periodontitis (11).

VI. CONCLUSION

Periodontitis and diabetes are highly prevalent, chronic, non-communicable diseases that present significant public health challenges in populations around the world. For several years now, the focus of dental professionals has been on establishing the close correlation between the two diseases and how to intervene to limit the effects of one on the other.

There are several studies in the literature on the influence of periodontal therapy, alone or in combination with antibiotic therapy, on the variation of metabolic values in diabetic patients, although the mechanisms of interaction between them are still not completely clear; even if we continue to study more and more closely how these diseases are related, we know that both influence each other, creating a cycle that is difficult to break.

From the analysis of the studies, the role that inflammation plays at the systemic level is fundamental, in fact, the elevation of inflammatory mediators (IL-1β, IL-6 and TNF-α) due to periodontal disease leads to increased insulin resistance with consequent elevation of blood glucose which results in higher HbA1c levels.

By intervening in periodontal inflammation through therapeutic protocols (hygiene education and SRP), it is possible to lower the levels of pro-inflammatory cytokines, which at a systemic level produce an increase in glycaemic values that in turn keep inflammatory parameters high.

Keeping the inflammatory state of the mouth under control is therefore beneficial for diabetic patients, especially those with uncontrolled or poorly controlled diabetes; it has been shown that those with poorly controlled diabetes benefit most from periodontal therapy.

To date, however, there is a lack of studies referring to the new classification and this leaves a door open for the future to better investigate the reciprocity of the two diseases in the light of the new targets.

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