Critical Review
Periodontology

What is the future of Periodontal Medicine?

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Abstract: In the last five decades, considerable progress has been made towards understanding the etiology and pathogenesis of periodontal diseases and their interactions with the host. The impact of an individual periodontal condition on systemic homeostasis became more evident because of this knowledge and prompted advances in studies that associate periodontitis with systemic diseases and conditions. The term Periodontal Medicine describes how periodontal infection/inflammation can affect extraoral health. This review presents the current scientific evidence on the most investigated associations between periodontitis and systemic diseases and conditions, such as cardiovascular diseases, diabetes, preterm birth and low birth weight, and pneumonia. Additionally, other associations between periodontitis and chronic inflammatory bowel disease, colorectal cancer, and Alzheimer's disease that were recently published and are still poorly studied were described. Thus, the aim of this review was to answer the following question: What is the future of Periodontal Medicine? Epidemiological evidence and the evidence of biological plausibility between periodontitis and general health reinforce the rationale that the study of Periodontal Medicine should continue to advance, along with improvements in the epidemiological method, highlighting the statistical power of the studies, the method for data analysis, the case definition of periodontitis, and the type of periodontal therapy to be applied in intervention studies.

Keywords: Periodontitis; Diabetes Mellitus; Cardiovascular Diseases; Pneumonia.

Introduction

Periodontal diseases are chronic inflammatory conditions of infectious origin that affect tooth-supporting tissues. They are classified as gingivitis and periodontitis. Although they are initially caused by microbial biofilm, environmental and genetic factors contribute to their development. Gingivitis is an inflammation of the gums originated by the biofilm of bacteria that is formed on the dental surface. However, periodontitis occurs due to untreated gingivitis, which proceeds to the loss of periodontal tissue, manifested by periodontal attachment loss and radiographically assessed alveolar bone loss. Several epidemiological studies from the

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1980s and the 1990s have shown that periodontitis can also have an impact on systemic health.[1]

The concept of focal infection, that is, the appearance of systemic disease as a result of a dental infection, was accepted until the middle of the 20th century, but due to the lack of scientific evidence at the time, this hypothesis was disregarded. In the late 1980s, some studies resumed interest in the association between periodontal diseases and other systemic diseases. With the evolution of knowledge about the pathogenesis of periodontal diseases, it was possible to identify their role in the rupture of systemic homeostasis.[2]

Over the past 30 years, many studies have assessed the association between periodontitis and systemic conditions/diseases, such as cardiovascular disease, diabetes, preterm birth and low birthweight, chronic lung diseases, and, more recently, chronic inflammatory bowel disease, colorectal cancer, and Alzheimer's disease. The term Periodontal Medicine has been defined to describe how periodontal infection/inflammation can affect extraoral health.

This paper describes the current scientific evidence regarding the knowledge about the most investigated associations between periodontitis and the aforementioned systemic conditions/diseases, in addition to presenting associations that have not yet been studied between periodontitis and other health conditions. Finally, this article seeks to answer the following question: What is the future of Periodontal Medicine?

Periodontitis and diabetes mellitus

As it is observed in large population surveys, people with diabetes, especially those who do not have it under control, are at high risk of periodontitis when compared to people who do not have diabetes.[3] On the other hand, observational studies have demonstrated the impact of periodontitis on the glycemic control of diabetes mellitus (DM).[4-7] Thus, the relationship between DM and periodontitis works in a two-way manner. As an infectious process, it is biologically plausible that periodontitis influences the metabolic control of people with diabetes.[8] High levels of inflammatory mediators expressed during the periodontal destruction process can negatively interfere with glycemic control.[8]

However, periodontal treatment can reduce the levels of these mediators, which suggests that the inflammatory state will be reduced, positively interfering in insulin regulation and leading to better glycemic control.[8,9] Although it is of great relevance, there is insufficient evidence about the effect of periodontal therapy in reducing glycemic levels in individuals with type 1 diabetes mellitus due to the lack of studies. However, clinical studies that generate better evidence like randomized clinical trials[10-17] or their meta-analysis[18] have been published to study the impact of periodontal therapy on the glycemic control of type 2 diabetes mellitus (T2DM).

Effect of periodontal therapy on diabetes control

The hypothesis raised by randomized controlled trials (RCTs) would be that periodontal treatment could contribute to better glycemic control in individuals with diabetes. The removal of bacterial deposits would reduce both the inflammation of oral tissues and the systemic inflammation burden caused by periodontitis, thus improving glycemic control. Periodontal treatment may initially play the role of an inflammatory stressor due to bacteremia and the rise of inflammatory markers, but in the long term it has beneficial effects on biochemical parameters related to systemic inflammation and risk factors for chronic diseases.[19]

Over time, RCTs have improved their methodological rigor and produced more reliable data and better evidence. A search for randomized clinical trials that were published in English and investigated the effect of periodontal treatment on the control of type 2 diabetes, with follow-up and a control group that did not undergo subgingival intervention in a timeframe of at least six months, identified eight studies (Table).[10-17] These studies have shown divergent results regarding the reduction of glycated hemoglobin (HbA1c). Two of these studies have shown a significant reduction in the mean level of HbA1c after six months in the group that received periodontal therapy when compared to a control group.[15,17] Two other studies have shown a

reduction in HbA1c in intra-group analyses when comparing the results of the initial period and the results of the follow-up after six months in the treated group;[11,13] however, no differences were observed between the groups of treated and untreated individuals. Conversely, the other four studies[10,12,14,16] did not observe a significant reduction in HbA1c at the follow-up, despite noticing that the periodontal therapy resulted in an improvement in the periodontal clinical condition. These results may be due to the methodological limitations of some of the published RCTs, including sample size problems, inclusion criteria, patients' clinical characteristics, results of periodontal therapy, and biased criteria for defining the presence of periodontitis.

In 2013, Engebretson et al.[12] published the study with the largest sample size ever carried out. There were no differences between the glycemic levels of individuals who received periodontal treatment and the control group without treatment.[12] This study, however, faced criticism due to the biases it presented.[20] Included patients had average glycemic levels close to the initial inclusion criterion (7%); 60% had HbA1c below 8% in the initial period; and a large proportion of obese individuals was included, which could mask the possible anti-inflammatory effects of periodontal treatment. Also, changes in periodontal clinical parameters after therapy were below the expectations considering the quality of the treatment performed.[20]

In the most recent study, D'Aiuto et al.[17] have evaluated over a year of observation of the effect of periodontal treatment, both non-surgical and surgical, when necessary, in 264 patients with T2DM and moderate to severe periodontitis. The patients were also subjected to strict hygiene control and supportive periodontal therapy every three months. The inclusion of patients was also more careful, with patients presenting at least 20 periodontal pockets bigger than 4 mm, alveolar bone loss greater than 30%, and at least 15 teeth in the dental arch. Over a year, a difference in glycemic levels was observed between the test group (HbA1c = 7.8%) and the control group (HbA1c = 8.3%), which did not receive treatment over the same period, only supragingival scraping and dental polishing, in the same periods in which the patients in the test group received active therapy. After an adjustment of age, sex, ethnicity, smoking habits, duration of diabetes, body mass index, and initial HbA1c level, the difference between the groups was 0.6% (95% CI: 0.3–0.9%), thus remaining significant. This reduction in HbA1c in individuals of the test group after 12 months was compared to the effect of adding a second antidiabetic drug to the conventional treatment. The active periodontal treatment employed proved to be effective, since after one year patients had an average of 27 periodontal pockets > 4 mm smaller (approximately 70%), as well as lower plaque rates (21%), bleeding rates (26%),

Table. Randomized clinical trials with at least 6 months of follow-up that evaluated the effect of periodontal treatment in type 2 diabetic patients. Comparison between groups that underwent periodontal treatment (test) or not (control).

Author (Country)	Sample		Periodontal treatment impact on glycemic control (HbA1c)
	n	Age (years)	
D'Aiuto et al.[17], 2018, UK	264	> 18	No difference at 6 months of follow-up; Significant reduction in HbA1c at 12 months of follow-up (-0.6%; -0.3 to -0.9; $p < 0.0001$)
Mizuno et al.[16],2017, Japan	28	≥ 30	No difference at 6 months of follow-up
Wu et al.[15], 2015, China	54	54.7 ± 5.64	Significant difference in HbA1c at 6 months between test group (7.41±0.20 to 7.09±0.12) and control (7.39±0.16 to 7.42±0.18); $p < 0,01$
Artese et al.[14], 2015, Brazil	24	≥ 35	No difference at 6 months of follow-up
Zhang et al.[13], 2013, China	71	35–80	No difference at 6 months of follow-up
Engebretson et al.[12], 2013, USA	214	≥ 35	No difference at 6 months of follow-up
Chen et al.[11], 2012, China	134	38–81	No difference at 6 months of follow-up
Katagiri et al.[10], 2009, Japan	49	39–75	No difference at 6 months of follow-up

and average depth gauge (0.8 mm) compared to the control group.[17] Two important points of this study can be mentioned. It was the study with the longer follow-up period after periodontal treatment, one year, and the therapy provided was based on the individual needs of the patients. Patients with good oral hygiene (dental plaque scores ≤ 20%) and at least one 6 mm or deeper residual periodontal pocket at 2 months had periodontal surgical therapy, while patients who still had suboptimum oral hygiene and patients who did not have residual 6 mm or deeper periodontal pockets received additional scaling and root planing.[17]

When evaluated together, it is difficult to reach a solid conclusion by compiling the results of these few studies, as they present high heterogeneity from the patient selection to the presentation of results.[10-17] A clear source of heterogeneity are the discrepancies in the characteristics of the samples in terms of HbA1c levels and for how long the individual had been diagnosed with diabetes at the beginning of the study. In some studies, glycemic levels that are close to the level of adequate control of diabetes may be attributed to the ineffectiveness of periodontal treatment in reducing glycemic levels, since the periodontal therapy would have little effect in a controlled patient with regular medication and a balanced diet because the low level of HbA1c would already be a non-changeable feature, considering that diabetes is a chronic disease with no cure yet.

Another issue that deserves attention is the different method adopted for case definitions of periodontitis,[21] since the patients' periodontal profile differs both in severity and in extension in the different studies. For example, Chen et al.[11] included patients with at least one site with loss of clinical insertion of 1 mm; in the study by D'Aiuto et al.[17] there were ≥ 20 periodontal pockets with probing pocket depths of > 4 mm and marginal alveolar bone loss of > 30%, and at least 15 teeth. For comparison, the second study presents a proportion of periodontal pockets ≥ 4 mm almost twice as big as the first (34% vs. 18%). These differences in the initial profile of the patients included in the studies can mitigate the real dimension of the effect of the treatment. The lack of rigorous inclusion criteria can lead to the inclusion of patients with a milder periodontal clinical condition, that is, a systemic inflammatory load that is also less intense as a result of periodontitis. Thus, the effects of the treatment could also be barely noticeable after periodontal therapy.

A systematic review with meta-analysis carried out by the Cochrane collaboration, updated in 2015,[18] pointed out that there was low-quality evidence that periodontal treatment, associated or not with the use of antimicrobials, improves the glycemic control of T2DM. This improvement resulted in an average reduction of 0.29% (95%CI: 0.10%–0.48%) of HbA1c, three to four months after the treatment. This is an important and clinically relevant result since the magnitude of HbA1C reductions in this short term obtained after periodontal interventions is similar to that frequently achieved by adding a second medication to a pharmacological regimen.[22]

However, there is insufficient evidence that these results are maintained after six months. Periodontal treatment results in an average percentage reduction of HbA1c of -0.02 (95%CI -0.20–0.16; p = 0.84). The quality of the evidence was low due to the high risk of bias and heterogeneity between studies.[18] Another important point is that the concomitant use of antibiotics with mechanical therapy might not be beneficial. It should be noted that at the time of publication of this meta-analysis, four studies previously cited had not yet been published[14-17] and were, therefore, not included here. Among these studies,[14-17] one had the greatest methodological robustness and another had the best results after one year of periodontal therapy follow-up.[17] The inclusion of those studies could modify the magnitude of the observed treatment, as well as the statistical significance of the results.

Identification of patients at risk for diabetes

A population-based study found that individuals with a self-reported family history of diabetes, hypertension, high cholesterol levels, and clinical evidence of periodontitis have a 27-53% probability of having undiagnosed diabetes.[23] The study by Lalla et al.[24] was able to identify 92% of patients with diabetes or pre-diabetes due to the presence of periodontal pockets greater than five mm associated with tooth

loss and the presence of HbA1c ≥ 5.7%. A recently published systematic review has shown that the prevalence of overall clinical assessment of diabetes in patients with periodontitis was 17.3 ± 4%, while in patients without periodontitis it was 11.0 ± 3.1%.[25] The odds ratio for individuals with periodontitis to be diagnosed with diabetes was 2.27 (95%CI 1.90–2.72).[25]

Therefore, it is possible that in addition to the treatment that may be important to improve glycemic control, the dentist may also contribute to the early diagnosis of the diabetic patient, thus contributing to the prevention of possible complications of the disease.

Tooth loss in diabetic patients

Because of the destruction of the tooth support apparatus, severe periodontitis can lead to tooth loss. Total or partial tooth loss is associated with poor DM glycemic control.[26,27] On average, adults with diabetes lose approximately twice as many teeth as those without DM, and one in five cases of edentulism in the United States is related to this disease,[27] resulting in significant effects on the oral and general health of people with diabetes. The loss of masticatory function as a result of tooth loss due to severe periodontitis can impact the nutrition of individuals and indirectly influence the glycemic control of those with diabetes.[28] Oral rehabilitation should be suggested to restore masticatory function.[22]

Future prospects

Periodontal treatment is suggested for the glycemic control of T2DM because of its benefits. If such reductions after periodontal therapy can be maintained over the long term, this can contribute to the reduction of morbidity and mortality associated with diabetes.[29] Studies that can generate better evidence (RCTs), with a better design, and that can correct biases of previous studies are still needed to better define the patient profile that can be most benefited and the magnitude of this benefit.

Despite limited evidence, it can be interpreted that periodontal treatment can contribute to better glycemic control of T2DM. It is a relevant and effective treatment to interrupt the process of destruction of the gingival tissues, control the present infection, keep the teeth in proper function, and prevent tooth loss. Patients with diabetes must be alerted to the possibility of developing periodontitis and also greater tooth loss. Likewise, patients with periodontitis should be warned that they are at a higher risk for diabetes. Thus, patients should be instructed to seek a periodontist for the correct diagnosis and appropriate treatment. Moreover, periodontists can play a very important role in the early identification of patients with diabetes.

Periodontitis and adverse pregnancy outcomes

In this section on the relationship between periodontitis and adverse pregnancy outcomes, three "landmark periods" will be addressed to present the evolution of this topic in the literature.

In the first period, the 1990s, the first studies on the subject emerged and, despite the methodological limitations at that time, investigations fulfilled their role as pioneers. During this period, Offenbacher et al.[30] developed the first epidemiological case-control study with women in the postpartum period, of which 93 had had premature children and/or children with low birthweight and 31 were controls, confirming the hypothesis that maternal periodontal disease is associated with this pregnancy outcome.[30] Other studies on the theme were also carried out, with highlights to Dasanayake,[31] who outlined an investigation with greater attention to confounding factors, developing a paired case-control study in 110 women, also in the postpartum period. Even then, Davenport et al.[32] advanced in terms of the statistical power of the study when they estimated a sample of 800 London women to test the hypothesis.[32] During this period, researchers faced challenges related to the epidemiological method, since there was no specific definition of periodontal disease for population-based studies. Despite this, these results contributed to strengthening Periodontal Medicine.

The second period, the 2000s, stands out for the high number of observational studies of different designs, such as cross-sectional, case-control, and cohort, with samples of different sizes, and definitions of periodontitis both dichotomously (presence or

absence of the disease) and continuously (with the use of periodontal parameters). In addition to that, there was an evaluation of numerous gestational outcomes that included low birthweight (< 2,500 g) or very low birthweight (< 1,500 g), premature birth (< 37 weeks, or extremely premature < 32 weeks), pre-eclampsia, and miscarriage and/or stillbirth. Although the method of these investigations has been diversified, in general, the findings of these studies have shown that there is a positive/moderate association between periodontitis and gestational outcomes. Scientific evidence from this period, composed of observational studies reviewed until May 2012 and summarized in the annals of a workshop held jointly by the European Federation of Periodontology and the American Academy of Periodontics, published in 2013, strengthened the biological plausibility of the association between periodontitis and gestational outcomes.[33]

Since then, findings have supported the theory that periodontitis promotes the hematogenous dissemination of the oral microbiota and its products, which directly reach the fetoplacental unit and induce immune-inflammatory responses. Indirectly, these inflammatory mediators produced in periodontal tissues, such as prostaglandin E_2 and tumor necrosis factor, reach the bloodstream and will impact the fetoplacental unit. They can also reach the liver and induce greater production of cytokines, including interleukin-6, and acute-phase proteins, such as C-reactive protein.[34]

Thus, according to the gestational period and the severity of the disease, periodontitis promotes undesirable pregnancy outcomes. Premature birth could be caused by exposure of the pregnant woman to less severe forms of periodontitis. Growth restriction and extreme prematurity would be due to exposure to more severe periodontitis and in an early gestational period. Even more serious exposures of periodontitis could induce spontaneous abortion, late abortion, and stillbirth.[34]

Still in the 2000s, in the annals of the aforementioned event, a review identified 13 randomized clinical trials on periodontal interventions and their effect on the occurrence of premature birth and low birthweight until July 2012.[35] The findings, obtained based on the quality and power of the investigations, suggested that non-surgical periodontal treatment in pregnant women did not reduce the risk of these outcomes.

In the third period, which concerns knowledge from the decade of 2010, studies reaffirm theories regarding biological plausibility between exposure to periodontitis and adverse pregnancy outcomes through direct and indirect pathways triggered by periodontopathogens, previously described, reinforcing that the direct route, that is, hematogenous transmission due to dental bacteremia, has remained the most accepted and the most investigated route in recent years. Also, exposure to oral infection is confirmed by the presence of microorganisms and their products in the fetoplacental unit, as well as serum and placental inflammatory biomarkers of the pregnant woman. This set of mechanisms would promote a metastatic infection, of a different extent, resulting in adverse pregnancy effects.[36]

As for the most recent epidemiological investigations on the subject, it appears that observational studies need improvement in methodological quality, by increasing the size of the samples evaluated, the appropriate definition of periodontitis for a younger population group, and an improved method of statistical analysis. Furthermore, it is also important to advance in a more comprehensive conceptual and theoretical model, with effective treatment of confounding covariables and evaluation of interaction factors, also called effect modifiers.

The relevance of modifiers in the association between periodontitis and adverse pregnancy outcomes was highlighted by Beck *et al*.[21] and encouraged methods of subgroup analysis to attribute greater validity and precision to the association measurements. The authors drew attention to the findings of Gomes-Filho *et al*.,[37] who studied the association between exposure to periodontitis and newborns with low weight in women with a normal level of HbA1c. In women with a high level of HbA1c, the association disappeared, with a possible influence of the maternal glycemic level on birthweight. Thus, specific woman-related factors that are not measured may account, in part, for the contradiction of the findings related to the hypothesis.

Regarding periodontal therapy, according to a Cochrane systematic review,[38] non-surgical

interventions during the second quarter of pregnancy are safe. Furthermore, there is poor-quality evidence that periodontal treatment can reduce low birthweight and there are not enough findings to determine which type of periodontal treatment is best. Despite the findings of better quality, randomized controlled trials point to the lack of effect of the treatment on the prevention of adverse pregnancy outcomes.[35,38,39]

These results show that only one type of intervention applied at a specific time during the gestational period of approximately 37 weeks is not able to change the outcome of the pregnancy. Nevertheless, it can be considered, at the level of biological plausibility, that, in the existence of periodontitis even before and during the gestational period, the pathogens would already be present in the fetoplacental unit and the effects of periodontal therapy during pregnancy to reduce bacteremia would not be enough to prevent the clinical condition that was already installed.

These findings by themselves do not demonstrate the inexistence of a causal relationship between infection/periodontal inflammation and adverse pregnancy outcomes. The period between the first clinical trial and the most recent is still short and many scientific advances need to be achieved for methodological improvement on this topic.

In this sense, the need for improvement in data analysis procedures must be highlighted. For example, Merchant et al.[40] reanalyzed data from the Obstetrics and Periodontal Therapy (OPT) randomized controlled trial,[41] which had not reported the effect of periodontal treatment on premature births. In this reanalysis, when considering miscarriages or stillbirths, which were more frequent in the control group, the therapy seemed to be beneficial to the participants. For this purpose, new epidemiological methods were employed, such as the survivor average causal effect (SACE), which corrected the potential bias resulting from unequal fetal survival in the treatment and control groups. Thus, the periodontal treatment provided to mothers with mild to moderate periodontitis, when done before the 21st week of gestation, prevented premature births.[40]

Thus, it seems plausible to consider the inclusion of periodontal treatment in a group of recommended procedures for preparing for pregnancy. In summary, the future of investigations related to periodontitis and adverse pregnancy outcomes must follow a path of incorporating the improvement of conceptual and methodological elements on the topic (Figure).

Cardiovascular diseases

The relationship between periodontitis and cardiovascular diseases (CVD) has been verified by epidemiological studies. A meta-analysis based on 22 case-control and cross-sectional studies presented an odds ratio of 2.35 (95%CI 1.87–2.96) for the existence of CVDs in patients with periodontitis.[42] This same meta-analysis, while evaluating solely longitudinal studies, concluded that the risk of developing CVDs was significantly higher in patients with periodontitis. And the relative risk observed was 1.34 (95%CI 1.27–1.42). More recently, after adjustments for potential confounding factors, severe periodontitis has been associated as an agent responsible for causing myocardial infarction exclusively in women, especially those under the age of 65.[43] A prospective study indicated an association between periodontitis and mortality in a homogeneous population of men aged between 60 and 70 years in Western Europe. The risk of death in men with greater loss of periodontal insertion was 1.57 (1.04–2.36) after adjustments for confounding factors (age, smoking, hypertension, BMI, cholesterol level, and previous history of cardiovascular events).[44] Sharma et al.[45] verified in a longitudinal study an association between periodontitis and increased mortality in individuals with chronic kidney disease.

Figuero et al.[36] identified bacterial DNA associated with periodontitis in atheromatous carotid plaques. These findings may offer additional evidence to support the association between periodontitis and CVDs. However, the mere presence of bacterial DNA does not imply that live bacteria would be present on atheromatous plaques. Moreover, additional studies should evaluate microbiological data on the atheromatous plaque and on the dental biofilm of these patients to confirm this direct relationship between periodontitis and CVDs. On the other hand, edentulism was associated with an increased risk of CVDs and mortality in postmenopausal women,

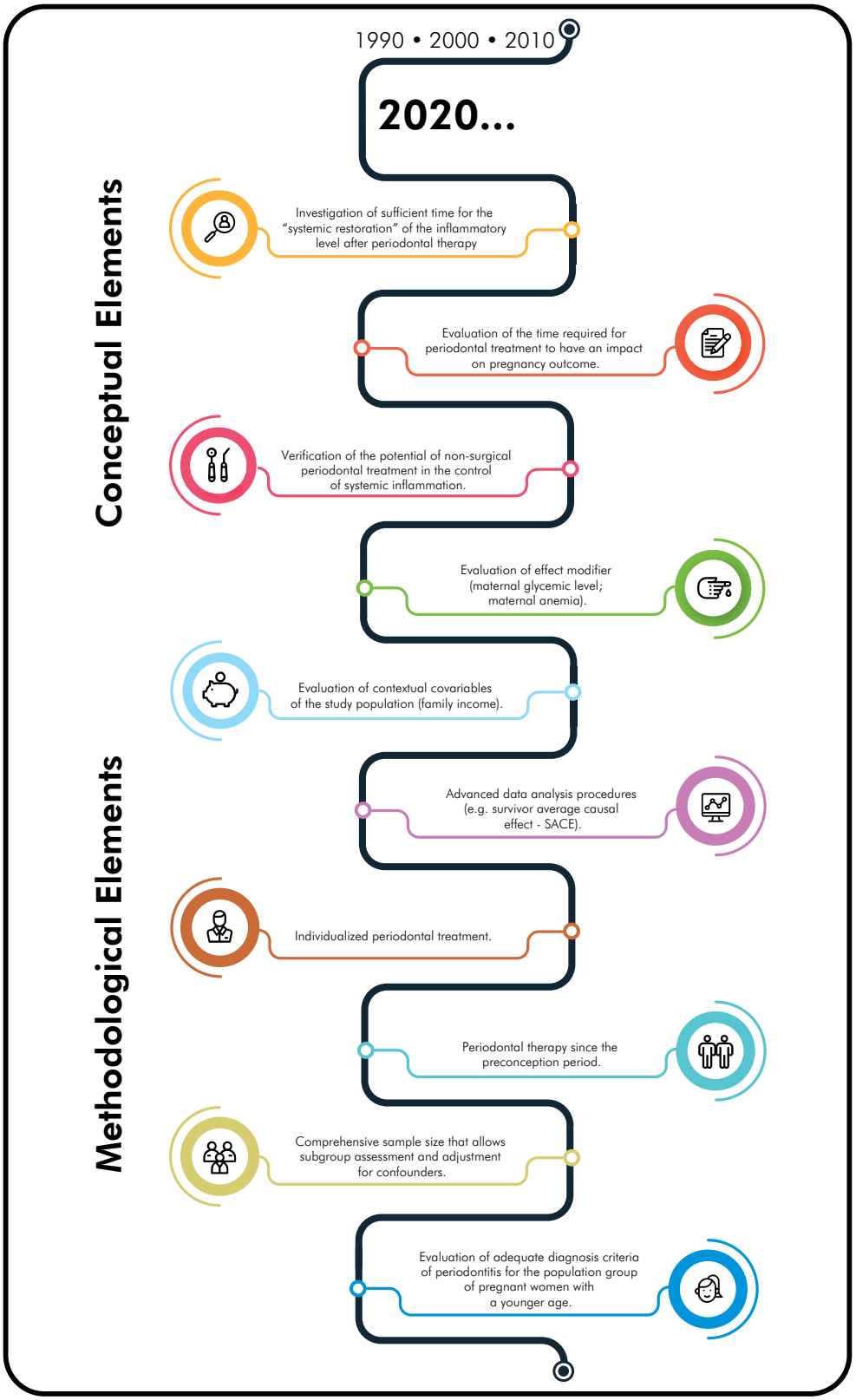

Figure. Possible future timeline for investigations into periodontitis and adverse pregnancy outcomes.

whereas the presence of self-reported periodontitis was associated with an increase in the mortality rate of such subjects.[46] Poor oral health, calculated by the number of remaining teeth, was related to the incidence of myocardial infarction and heart failure over an average length of time of 15.8 years. However, such association was not related to stroke occurrence, which suggests that oral health is not related in the same manner to the main cardiovascular disorders.[47]

While several studies have pointed out an association between periodontitis and CVDs, others have not shown such an association. Several factors have contributed to these conflicting results, like different study designs, great variety in the size of the samples, and more, which results in substantial differences concerning their statistical powers and in difficulties in establishing a consensus on the definition of periodontitis as an exposure. The use of numerous diagnostic criteria makes comparing and interpreting the results of different studies a difficult task. Clinical parameters such as bleeding on probing, depth of pocket on probing, clinical level of insertion, bone loss, and tooth loss were used as markers of periodontitis. Periodontal evaluation often included the use of partial indices. Partial indices (CPITN) and questionnaires underestimate the true extent and severity of the periodontal disease and can lead to misdiagnosis. In addition to these factors, the control of confounding factors may vary, with different parameters being used in each study. Additionally, most longitudinal studies evaluated only the prevalence of periodontitis and its relationship with future cardiovascular outcomes.

The incidence of periodontitis was significantly associated with an increased risk of cardiovascular events.[48] The association between the prevalence of periodontitis and the incidence of CVDs can be mitigated by performing periodontal treatment over the years of follow-up. However, despite all the differences mentioned above, meta-analysis demonstrated a mild to moderate association between periodontitis and CVDs.[42,49]

Studies evaluating the effect of periodontal treatment are key to determine the causal relationship between periodontitis and CVDs. The idea is that randomized clinical studies demonstrate a decrease in the "effect" (cardiovascular events) by eliminating the "cause" (periodontitis). Such evidence, so far, does not exist. Conducting this type of study is difficult, since many challenges must be overcome, like sample size, follow-up time (with all associated ethical problems), presence of comorbidities, concomitant medications, effective periodontal treatment, and periodontal maintenance. A sample calculation simulation for this type of study illustrates the magnitude of the issue. Approximately 9,600 patients per group would be required to demonstrate a 20% relative risk reduction of a second heart attack in patients who received periodontal treatment after the first heart attack when compared to patients who did not receive periodontal treatment, with $\alpha = 0.05$ and $\beta = 0.10$.[50]

Studies investigating the effects of periodontal treatment have mainly focused on two aspects: evaluations of soluble biomarkers, such as C-reactive protein (CRP) and LDL cholesterol, and the use of imaging technologies, such as the thickness of the intima-media of the carotid artery and ultrasound of the brachial artery. Additionally, some studies have evaluated the relationship between dental treatment and reduced risk of cardiovascular events.

Several studies have evaluated the impact of periodontal treatment in reducing blood levels of inflammatory substances, which are considered to be risk markers for CVDs. Patients with periodontitis have higher levels of CRP when compared to healthy controls.[51] The magnitude of this difference is clinically significant, since it is high enough to place them at levels of greater risk for CVD. D'Aiuto et al.[19] conducted one of the first studies evaluating the effect of periodontal treatment on systemic inflammation and exposed that periodontal therapy resulted in a dose-dependent decrease in serum CRP levels. A meta-analysis has shown that periodontal treatment decreased serum levels of CRP by about 0.5 mg/l.[52] In a 6-month randomized clinical study, Caúla et al.[53] demonstrated that periodontal treatment reduced serum levels of CRP by 50%. Other studies have indicated that periodontal treatment significantly decreased serum CRP levels in patients suffering solely from periodontitis and other associated diseases, such as chronic kidney disease and refractory arterial hypertension.[54,55] Thus, periodontal treatment can reduce CRP levels for the

low cardiovascular risk category. These findings are important since high levels of CRP are excellent predictors of the development of atherosclerosis, AMI, and death. Another strong risk marker for CVDs is fibrinogen, which is associated with the development or presence of atherothrombosis. Its levels are also significantly reduced after periodontal treatment. A study carried out by our group demonstrated a significant reduction in fibrinogen levels in patients with periodontitis and refractory arterial hypertension after periodontal therapy.[56,57]

Circulating levels of proinflammatory cytokines are also higher in patients with periodontitis when compared to healthy patients. The same is also true when comparing patients with CVDs and periodontitis and those who suffer solely from CVDs. Although several studies point to significant effects of periodontal treatment in reducing the levels of pro-inflammatory cytokines, the results are still very controversial. The difficulty in accurately measuring the levels of cytokines in the blood may contribute to this condition. Cytokines in the blood are linked to other proteins and only a small portion of the total can be detected, since commonly used tests detect only their unbound fractions.[58] However, significant reductions in IL-6 and TNF-α occur after periodontal treatment.[59]

Dyslipidemia is one of the main modifiable risk factors for CVDs. Several lipid markers have been identified as traditional biomarkers associated with CVDs, including LDL and HLD cholesterol, total cholesterol, and triglycerides. Numerous studies have shown that reductions in LDL levels are associated with decreases in cardiovascular risk. The magnitude of the reduction in cardiovascular events is related to the extent of LDL reduction, with each decrease of 40 mg/dl (1 mmol/l) corresponding to a 24% reduction in cardiovascular events.[60] Likewise, the increase in HDL has been associated with a decrease in cardiovascular risk. Each increase of 1 mg/dl (0.03 mmol/l) in HDL is associated with a 2 to 3% reduction in the risk of future coronary heart disease.[61] A meta-analysis has discovered significant improvements in total cholesterol and HDL levels after periodontal therapy. Interestingly, patients with periodontitis and comorbidities are those who benefit the most from improvements resulting from periodontal treatment.[59]

Hypertension is widely recognized as a risk factor for cardiovascular events. Periodontitis is associated with a higher risk of high blood pressure. In addition, the management of periodontitis can influence the management of hypertension. The outcomes of CVDs may be better if the poor oral health of the general population is taken into account.[62] On the other hand, a reduction of 7 mmHg in systolic blood pressure was observed two months after intensive periodontal treatment. This reduction was more pronounced in smoking patients.[63] Reductions of 12.5 mmHg and 10 mmHg in systolic and diastolic pressures, respectively, have been reported after periodontal therapy in patients with refractory arterial hypertension, in addition to a reduction in left ventricular mass.[57] This reduction is equivalent to the introduction of another medication for the control of hypertension. A meta-analysis has shown that a reduction of 10 mmHg in systolic pressure and 5 mmHg in diastolic pressure, with the use of any of the main classes of antihypertensive drugs, reduces cardiovascular events (fatal and non-fatal) by about 25%, stroke by about 33%, and heart failure by about 25% as well.[64] Czesnikiewicz-Guzik et al.[65] evaluated the effect of periodontal treatment in patients with arterial hypertension through a 2-month randomized clinical study. The group that received periodontal treatment had a significant reduction in systolic blood pressure (mean difference of -11.1 mmHg; 95%CI 6.5–15.8; $p < 0.001$), correlating with an improvement in periodontal status. Diastolic pressure and endothelial function also improved after periodontal treatment. These cardiovascular improvements were accompanied by reduced levels of IFN-c and IL-6.[65]

Patients with chronic kidney disease present an increased risk of death originated by problems associated with atherosclerosis. The increase in CRP levels is a risk indicator for the progression of atherosclerosis in this group of patients, especially patients on pre-dialysis and hemodialysis. Brito et al.[66] have shown that periodontitis was associated with high levels of CRP in pre-dialysis and hemodialysis patients. On the other hand, periodontal treatment in pre-dialysis patients improved the glomerular filtration rate, indicating an improvement in renal function.[67]

Another common target of periodontal pathogens and circulating cytokines is the endothelium, which plays a central role in the regulation of vascular homeostasis. The reduction in endothelium-dependent vascular reactivity characterizes the condition of endothelial dysfunction, which is currently considered the initial stage for the development of atherosclerosis.[68] Studies have shown that periodontitis was associated with endothelial and microvascular dysfunction.[69,70] Tonetti et al.[71] evaluated the effect of periodontal therapy on endothelial dysfunction. Systemically healthy patients with severe generalized periodontitis were randomized into two treatment groups: control (supra-gingival scraping), and test (periodontal therapy). Six months later, the group that received periodontal therapy showed a significant improvement in endothelial function. In the control group, there was no change in endothelial function. The treatment effect was dose-dependent, with a significant correlation between the reduction in the number of periodontal pockets and bleeding on probing and improvement in endothelial function. Similar results were found in patients with hypertension and CVD.[56,70,72]

The first signs of carotid atherosclerosis are usually measured by the thickness of the intima layer of the carotid arteries. This measure receives considerable attention, since it is highly correlated with diseases in the carotid arteries and is considered a good predictor of cerebral and ischemic cardiovascular events. An increase in this thickness occurs in patients with periodontitis, even in early stages, without clinical evidence of atherosclerosis. Patients with refractory arterial hypertension who received periodontal therapy significantly reduced the values of intima-media thickness after six months.[56] A recent randomized clinical trial has also shown a significant reduction in the thickness of the intima-media after periodontal treatment.[73]

So far, concrete data on the effects of treatment on cardiovascular morbidity and mortality do not exist. Paju et al.[74] evaluated 141 patients with acute infarction or unstable angina who participated in a controlled clinical trial using clarithromycin for three months. According to the authors, antibiotic therapy would have an impact on the progression of chronic infections, including periodontitis, and could result in a reduction in cardiovascular events. After an average follow-up of 519 days, the authors noted that the use of clarithromycin was not beneficial in preventing recurrent cardiovascular events in patients with periodontitis compared to healthy patients. A pilot study with 303 participants was conducted to assess the feasibility of a secondary prevention clinical trial to investigate whether periodontal treatment reduces the risk of CVD. After 25 months of follow-up, the frequency of adverse cardiovascular events was similar between the group that received periodontal treatment (oral hygiene instruction and scaling, and root planing using a piezoelectric ultrasonic scraper) and the group that received community care (oral hygiene instruction and referral letter to seek periodontal treatment).[75] It is worth mentioning that all patients had their teeth with poor prognosis extracted before randomization. Of the patients assigned to the community care group, 48% received periodontal or preventive treatments.[76]

On the other hand, Lee et al.[77] demonstrated that patients with periodontitis who received treatment had a lower risk of stroke. Regular use of dental services (dental care at least once a year) was also associated with a reduced risk of stroke over 15 years of follow-up.[78] Holmlund et al.[79] reported that patients who did not respond satisfactorily to periodontal treatment, which means they presented > 10% of periodontal pockets > 4 mm and ≥ 20% of sites with bleeding on probing one year after active treatment, had an increased risk of CVDs during a median follow-up of 16.8 years.[79] Interestingly, hemodialysis patients who received intensive periodontal treatment had a 22% reduction in the risk of CVD.[80]

A recent study based on data from an insurance company retrospectively tested the hypothesis that periodontal treatment would reduce medical costs and hospitalizations for five years after treatment in patients with some systemic conditions. Significant reductions in medical costs and hospitalizations were observed in patients with coronary artery diseases and cerebrovascular diseases.[81] According to a systematic review, no study investigating the primary prevention of CVDs in patients with periodontitis has been found. The only secondary prevention study found had a high risk of bias. Therefore, the evidence found was

insufficient and of low quality to support or refute the role of periodontal therapy in preventing CVD recurrence in patients with periodontitis.[82]

Oral health status and pneumonia

It has been known for some time that poor oral health and the oral microbiome and oral inflammation it entails play an important role in the pathogenesis of several respiratory diseases, particularly pneumonia, but also chronic obstructive pulmonary disease and asthma.[83] Based on this knowledge, multiple oral interventions have been explored to prevent respiratory infections in high risk patients. This section of this article, which will review the role of poor oral health in lower respiratory infections, is a synopsis of a recently published article that summarized the role of the oral cavity in lower airway infection.[84]

Pneumonia, the inflammatory condition of the lung parenchyma initiated by aspirated microorganisms into the lower airways from proximal sites like the oral and nasal cavities, is a common disease causing significant morbidity and mortality. Pneumonia is classified according to the location of the origin of the etiologic infectious agents (i.e., from the community vs. from within a healthcare institution, the so called nosocomial pneumonia). Pneumonia and influenza together are major causes of death[85] and are associated with substantial morbidity and economic cost.[86] Hospital acquired infections (HAP) are those that occur > 48 hours after admission to a hospital or other residential healthcare facility (such as a nursing home). Most patients who contract HAP are infants, young children, and persons > 65 years of age; persons with severe underlying disease, immunosuppression, neurological deficit; and patients undergoing abdominal surgery. HAP can be further divided into two subtypes: ventilator-associated pneumonia (VAP) and non-ventilator-associated pneumonia (NV-HAP).[87,88] Pneumonia is the most common infection in the intensive care unit (ICU) setting, accounting for 10% of infections in ICUs.[89]

Poor oral health status has been associated with the pneumonia etiology. As a result, there has been considerable interest to determine whether oral care can interrupt the process of lung infection to prevent the disease, especially in high risk groups such as the elderly and hospitalized patients.[90]

A complex microbial community resides on the surfaces of the lower airways of healthy subjects.[91] The use of sterile bronchoalveolar lavage sampling techniques has allowed examination of the lower airway in healthy subjects, who are now known to harbor small populations of bacteria. The evidence to date suggests that dispersal of microbes from the oral cavity is the primary driver of the healthy lung microbiome.[92] Pneumonia patients often harbor multiple species of bacteria and microbes that are normally indigenous to the oral cavity.

The oral cavity serves as an important reservoir of lung infection, particularly in high risk subjects like mechanically ventilated and elderly nursing home patients. When a patient is ventilated, an endotracheal tube is placed through the oral cavity into the lower airway to provide oxygen into the lower airway, and the tube often becomes colonized with microbes from the oral cavity, which subsequently form a biofilm and promote VAP. A "microbial shift" occurs in the dental plaque of ventilated patients, with colonization by potential VAP pathogens that seed the lower airways via endotracheal tube biofilms.[93] Molecular epidemiology techniques have been used to demonstrate that respiratory pathogens isolated from the lung are genetically indistinguishable from strains of the same species isolated from the oral cavity in hospital patients who receive mechanical ventilation.[94,95] Another study used molecular techniques to assess the impact of oral hygiene status on the composition of the microbiome of the bronchoalveolar lavage fluid (BALF) directly obtained from lungs suspected to have pneumonia. Poor oral hygiene was found to be significantly associated with anaerobes in the lungs of patients with pneumonia.[96]

Metataxonomics, a recently developed approach to assess microbial diversity that uses data from high-throughput sequencing to identify microorganisms and viruses within a complex mixture, found no significant differences in the microbial communities between the microbiome of dental plaque, endotracheal tubes (ETTs), and non-directed bronchial lavages (NBLs) in mechanically ventilated patients' samples,

and most bacteria detected were oral species and respiratory pathogens (*Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae, and Haemophilus influenzae*).[97]

Poor oral health is also connected to aspiration pneumonia, especially in the case of nursing home residents.[98-100] There is also some evidence that periodontal disease may be associated with risk for pneumonia in elderly patients. A study of an elderly Japanese population found that the adjusted mortality due to pneumonia was 3.9 times higher in persons with 10 or more teeth with a probing depth exceeding 4 mm (i.e., with periodontal pockets) than in those without periodontal pockets.[101] A case-control study compared 85 cases with nosocomial pneumonia against 230 controls without nosocomial pneumonia, employing a full-mouth periodontal examination of all subjects.[102] Individuals with periodontitis had a three-fold excess risk pneumonia compared to the control group without periodontal disease, following adjustment for a variety of potential confounding variables. It has also been suggested that the number of teeth may also impact the risk for pneumonia, with a direct relationship between number of teeth lost and pneumonia reported.[103]

Taken together, these and other published findings suggest that oral biofilm is an important reservoir for the microbes that are aspirated into the lower airway and attach to the endotracheal tube.

In light of these findings, oral hygiene or periodontal therapy could help prevent the onset or progression of pneumonia in high-risk patients. Several studies have evaluated the effectiveness of oral care to prevent pneumonia in nursing home patients; for example, mechanical oral care, in some cases in combination with povidone iodine, has been shown to have a moderate effect in reducing the risk of pneumonia in nursing home residents.[104-107] A recent study has shown that the loss of oral self-care ability along with gender (male) and malnutrition can increase the risk of pneumonia in elderly patients.[108] In addition, once-a-week professional oral cleaning significantly reduced influenza infections in an elderly population.[109]

Implementation of professional oral care programs in nursing facilities, involving the use of dental hygienists to provide direct oral care, including tooth, tongue, and denture brushing, may help reduce the oropharyngeal microbial burden and therefore the number of microbes that can be aspirated into the lower airway.[110] Such an approach may also reduce the risk of other respiratory infections, like influenza.[111] This idea is supported by a recent systematic review that reported evidence that oral care interventions given by dental personnel in elderly adults were more effective on mortality from HAP than oral care interventions given by nursing personnel in hospitals and in nursing homes.[112]

Some studies have not supported the effectiveness of oral care to prevent pneumonia in nursing homes.[113] A unique cluster-randomized study of 834 nursing home patients, followed over the course of a year, has shown no benefit of a comprehensive oral care program, which included tooth brushing, topical chlorhexidine, and upright positioning during feeding. The lack of effect could be explained by several possibilities, including less than ideal staff adherence to the intervention protocol, control home usual oral care may have been modified after study initiation to more closely resemble the intervention arm, or changes in the microbial flora over time in response to the implementation of the intervention.

Overall, oral cleansing protocols have been shown to reduce pneumonia in both edentulous and dentate subjects, suggesting that oral colonization of bacteria contributes to nosocomial pneumonia to a greater extent than periodontitis *per se*. However, intervention studies where periodontitis is treated on the incidence of pneumonia have not been performed due to the complexities imposed by ICU or bed-bound nursing home patients. It has been suggested that dental services are underutilized by nursing home residents. Thus, more effort must be made to improve the frequency and effectiveness of oral care protocols in nursing homes.[114]

More recent associations between periodontitis and other diseases

Despite the tremendous progress made by periodontal medicine since the early 1990s, new associations and, more importantly, the elucidation

of the biological mechanisms for such associations continue to emerge. A systematic review conducted in 2016 revealed that periodontitis has been linked to 57 other systemic diseases.[115] Periodontal medicine has been shown to be quite dynamic and in constant evolution, however, a future challenge will be to demonstrate convincingly that the prevention and treatment of periodontitis will bring significant benefits to other diseases.[116]

Among the associations that have gained more attention recently, we can highlight inflammatory bowel disease, several types of cancer, and Alzheimer's disease. In this sense, the interrelation between the oral and intestinal ecosystems appears as a new frontier for periodontal medicine. Changes in the oral microbiota concerning oral and systemic diseases have been the focus of constant investigation.[117,118] Several reports have shown that microorganisms from the oral cavity can overcome physical and chemical barriers and colonize other sites, potentially contributing to the emergence and/or aggravation of other diseases. Studies have shown the growth of oral bacteria in the intestinal microbiota of patients with several diseases.[119,120,121] Experimental studies have shown that oral administration of *P. gingivalis* causes changes in the intestinal microbiota and intestinal epithelial barrier, together with changes in the liver and adipose tissue.[122,123] In line with these findings, individuals with periodontitis have shown changes in the intestinal microbiome, such as less diversity and an increase in the *Firmicutes* / *Bacteroidetes* ratio.[124]

Epidemiological studies have shown that individuals with inflammatory bowel disease were more likely to have periodontitis.[125] On the other hand, the presence of periodontitis increased the risk of developing ulcerative colitis, one of the types of inflammatory bowel disease, over a 13-year follow-up.[126] Despite limited epidemiological evidence pointing to periodontitis as a possible risk factor for inflammatory bowel disease, substantial studies in animal models are beginning to point out the possible biological mechanisms by which periodontal disease and oral pathogens contribute to inflammatory bowel disease. Oral bacteria have been shown to colonize and persist in the intestine, activating the immune system and causing chronic inflammation in a susceptible host. *Klebsiella* strains isolated from saliva can induce a strong T helper 1 cell response in the intestine in the context of intestinal dysbiosis and induce colitis in genetically susceptible hosts.[127] More recently, it has been shown that oral pathobionts, including *Klebsiella* species, increase their number in periodontitis and can trigger an inflammatory response in the intestine through two mechanisms. First, when colonizing the intestine, oral pathobionts activate the local immune system, triggering the production of IL-1β and colitis. Second, T helper 17 cells that appear during periodontitis can migrate to the intestine and be activated by oral pathobionts that colonized the intestine and lead to the development of colitis.[128] These discoveries reveal new mechanisms of how periodontitis can influence other pathogenic processes in sites far from the oral cavity and open new paths for investigating the clinical and therapeutic impact of periodontitis.

The role of the oral microbiota in the development of cancer, especially *Fusobacterium nucleatum* and colorectal cancer, has been the focus of research and has recently been reviewed.[129] This relationship is based on the premise that periodontitis facilitates bacterial translocation to other parts of the body, where dysbiosis, chronic inflammation, and breaking of the epithelial barrier synergize to favor carcinogenesis.[129] Recent evidence that analyzed paired samples of saliva and colorectal cancer suggested that the origin of *F. nucleatum* in cancerous tissue is the oral cavity and that the hematogenic pathway may be the preferred one for its dissemination and colonization of the tumor.[130] Also, an increase in *Fusobacterium* spp. has been observed in colon adenoma compared to healthy adjacent tissue, as well as in the feces of patients with adenoma and colorectal cancer compared to healthy controls,[131] and the amount of *F. nucleatum* DNA in cancerous tissue is positively associated with the specific mortality from colorectal cancer.[132] As for the mechanisms for such an association, *F. nucleatum* inhibits the cytotoxicity of NK (natural killer) cells and the activities of lymphocytes that infiltrate the tumor tissue through the interaction of bacterial protein Fap2 with the TIGIT receptor.[133] Similarly, associations with other types of cancer have also been proposed, for example, with lung and pancreatic cancer.[129,134] It is

noteworthy that the existing epidemiological evidence points mainly to a positive association between periodontal disease and cancer risk, however, it still lacks more robust analyses.[134]

Another aspect of periodontal medicine that has gained a lot of attention in the last decade is the relationship with neurodegenerative diseases, particularly Alzheimer's disease, in which evidence indicates that periodontal disease can induce systemic inflammation, disruption of the blood-brain barrier, degeneration, and cognitive impairment.[135] Epidemiological studies show an association between periodontitis and Alzheimer's disease.[136,137] A *post-mortem* analysis of brain tissue has shown that *Treponema* species were detected more frequently and in greater proportions in Alzheimer's patients than in controls.[138] Furthermore, a positive association has been demonstrated between loss of clinical insertion and accumulation of amyloid in the brain of cognitively normal elderly people.[139] Studies *in vitro* and in animal models have provided biological plausibility for such a relationship. For example, DNA from *P. gingivalis* and gingipains was found in the brain affected by Alzheimer's disease, and oral administration of gingipain inhibitors in an animal model was able to reduce the load of *P. gingivalis* in the brain, the production of β amyloid, and neuroinflammation.[140] However, the clinical impact of such inhibitors on the management of neurodegeneration deserves careful investigation.

Final considerations

According to the most recent scientific evidence, Periodontal Medicine is a significant topic in dental and craniofacial research and should continue to advance, since in many areas the time of investigation makes the topic still very incipient and "underexplored". Therefore, improvement of the epidemiological method is necessary through conceptual and methodological elements.

In this sense, the power of studies can be emphasized. The studies must be presented with sufficient sample sizes so that it is possible to evaluate several confounder and modifier covariables, as well as to allow advances in the methods of data analysis. As for the confounding factors, the importance of incorporating conceptual theoretical models related to the socioeconomic condition of the studied populations is also emphasized. Regarding the modifying covariables, the sample needs to be of a scope that allows it to be divided into subgroups, without losing the power of the studies.

The full-mouth periodontal examination is essential for defining periodontitis cases, since association studies need the diagnosis of the periodontal condition to have greater specificity. That should also help avoid the incorporation of false-positive diagnoses that will influence the magnitude of the association between periodontitis and the outcome under investigation. Also, it is crucial to improve the type of periodontal therapy used in interventional studies, advancing towards the possibility of individualized periodontal treatment.

Thus, the future of Periodontal Medicine must follow paths that are increasingly closer to the continuous advances in the epidemiological method, considering that the individual with periodontitis may present a hyperinflammatory phenotype, a common condition, concomitant with other chronic diseases, and this oral condition is the signal for the diagnosis of the "inflamed individual".

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