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Received: 27 July 2023 | Revised: 21 September 2023 | Accepted: 23 September 2023

DOI: 10.1111/prd.12536

Periodontology 2000 WILEY

REVIEW ARTICLE

Periodontitis and metabolic diseases (diabetes and obesity): Tackling multimorbidity

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1 | INTRODUCTION

Noncommunicable diseases (NCDs) are long-term chronic conditions that result from a combination of genetic, physiological, environmental, and behavioral factors. They include a vast range of diseases such as cardiovascular diseases, kidney, liver and respiratory diseases, cancers, plus those underpinning the focus of this article, periodontitis, and metabolic diseases (diabetes and obesity). NCDs represent a particular burden to health-care systems worldwide as they are controlled rather than cured, therefore requiring long-term care. Furthermore, they account for approximately 41 million deaths (71%) globally each year[1] with mortality predicted to rise to 52 million deaths worldwide by 2030 NCDs.[2]

Between 1990 and 2010, severe periodontitis was the sixth most prevalent chronic condition in the world, with a prevalence of 11.2%[3]; more recent data from the World Health Organization (WHO) highlight the current prevalence of severe periodontitis to be approximately 19%.[1] With regard to diabetes, data from the systematic analysis of the Global Burden of Disease Study 2021 revealed that the age-standardized prevalence of diabetes rose from 3.2% in 1990 to 6.1% in 2021.[4] Similarly for obesity, classified as WHO Body Mass Index (BMI) ≥25 kg/m^2, the prevalence increased from 28.8% in 1980 to 36.9% in 2013 in men, and from 29.8% to 38.0% in women.[5] With the exponential increase in NCDs, the occurrence of individuals presenting with more than one chronic disease is also rapidly rising. "Multimorbidity," defined as the presence of two or more long-term physical or mental disorders, is now considered a worldwide epidemic, with a recorded prevalence of over 20% in the adult population.[6]

Periodontitis, diabetes, and obesity, all chronic inflammatory diseases, are an example of multimorbidity highly relevant to dental practitioners. The relationship between diabetes and obesity has been increasingly researched and accepted over the last decades. Thirty years ago, scientific evidence of the association between periodontitis and diabetes was in its infancy, however, scientific investigation, with important contributions by European researchers, has confirmed the bidirectional association of these two diseases. Subsequently, as obesity had became recognized as an NCD, further evidence has emerged supporting the association of periodontitis with obesity.

Over the last 30 years, the management of NCDs has dramatically advanced and changed in approach as evidence of the important role of common risk factors has emerged, therefore going from a medication-based treatment to a more comprehensive approach including behavior change interventions for risk-factor modifications.[7] The increasing prevalence of NCDs, despite improved treatments and the global efforts to tackle them, suggests this alarming rise may be due to the simultaneous advent of the "modern lifestyle", which is characterized by the increased consumption of ultra-processed foods as well as smoking and alcohol, long sitting hours, and the combination of high stress and poor sleep quality.[8–10]

As will be outlined in this review, unhealthy lifestyles have repercussions on overall general health as they act upon the common shared biological mechanisms of systemic inflammation, insulin resistance, and immune function, eventually leading to the onset of NCDs and the development of multimorbidity. As such, the "single-disease" framework within which health-care systems as well as medical research and education has been configured over the last decades should shift toward a "multiple-disease" framework encompassing a comprehensive and multidisciplinary approach to effectively manage multimorbidity. This narrative review discusses the three-way relationship between periodontitis and metabolic disease (diabetes and obesity) with the aim to suggest new strategies to tackle multimorbidity in the medical and dental settings.

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2 | THE THREE-WAY RELATIONSHIP AMONG PERIODONTITIS, DIABETES, AND OBESITY

Over the last three decades, a large body of epidemiological and meta-epidemiological evidence has been published in support of the multimorbid occurrence of periodontitis, diabetes, and obesity. Similar with other chronic diseases, periodontitis, diabetes, and obesity prevalence, progression and treatment outcomes are influenced by common risk factors and share similar biological mechanisms as summarized in the following sections.

2.1 | Bidirectional relationship between periodontitis and diabetes

2.1.1 | Observational evidence

The most recent meta-epidemiological data on the bidirectional association between periodontitis and diabetes based upon 15 cohort studies with an average follow-up of 9–11 years, highlighted a 56% higher risk of diabetes incidence in individuals with periodontitis (vs no periodontitis; RR = 1.26; 95% CI: 1.12–1.41) and a 55% higher risk of periodontitis incidence in those with diabetes (vs no diabetes; RR = 1.24; 95% CI: 1.13–1.37). These associations remained consistent in subgroup analyses by type of diabetes, duration of follow-up with adjustment for relevant confounders, such as smoking status and education.[11,12]

2.1.2 | Experimental evidence

The consistency of this bidirectional association has also been highlighted by recent meta-analytical data on the systemic effects of periodontal treatment on diabetes, with specific focus on type 2 diabetes mellitus (T2DM).[13–15] Orlandi and colleagues conducted a systematic review and meta-analysis to investigate the overall systemic effects of periodontal treatment; at 6-months follow-up, periodontal therapy was reported to reduce the concentration of fasting plasma glucose (MD = −1.09; 95% CI: −1.96, −0.21) and markers of systemic inflammation (hs-CRP MD = −0.55; 95% CI: [0.84, −0.27] and IL-6 MD = −0.48; (95% CI: −0.88, −0.08)). In addition, the most recent available meta-analytical data[15] resulted from studies performed in a variety of geographical locations, including the United Kingdom,[16] China,[17] and the United States.[18] The meta-analysis summarized the results from 12 randomized controlled trials with at least 6 months follow-up and demonstrated that subgingival instrumentation resulted in 0.29% (95% CI: 0.10–0.47) lower glycated hemoglobin (HbA1c) levels when compared to nonactive treatment. Although a high heterogeneity across studies was found, the overrepresentation of females in the included studies and a diagnosis of diabetes prior to 8.5 years before may explain this variability.[15]

Similarly, diabetes control, achieved mainly through dietary counseling and oral health education, was shown to be associated with the improvement of periodontal clinical parameters, such as bleeding on probing, probing depth, and clinical attachment level, over a follow-up period ranging from 4 weeks to 6 months after the intervention.[19] The results of this systematic review contributed to the recommendation in the most recent EFP guidelines for the treatment of Stage I–Stage III periodontitis suggesting diabetes control interventions in patients undergoing periodontal therapy.[12] Furthermore, the most commonly prescribed oral antihyperglycemic drug for diabetes treatment, metformin, was demonstrated to reduce periodontal bone loss in a rat-model ligature-induced periodontitis.[20] Randomized clinical trials have also been performed to assess whether locally delivered metformin gels could ameliorate clinical periodontal parameters. Overall, results showed a significant beneficial adjunctive effect of locally delivered metformin in terms of PD reduction and CAL gain when compared to either subgingival instrumentation or open flap debridement alone.[21,22]

2.2 | Bidirectional relationship between periodontitis and obesity

2.2.1 | Observational evidence

A large body of epidemiological, including cross sectional and longitudinal studies, and meta-epidemiological evidence, has shown a significant association between obesity and periodontal diseases in children, adolescents, and adults.[23] Obesity is associated with increased risk for onset of periodontitis, increased severity of disease in those with periodontitis and poorer outcomes following periodontal treatment.[24] Specifically, in a case–control study conducted on 286 participants, overweight/obesity was associated with 3-time increased odds of a periodontitis diagnosis irrespective of age, gender, ethnicity, smoking status and dental plaque levels.[25] The association with severity and treatment outcomes has shown a dose–response relationship between BMI and periodontitis[26–28] and, likewise, high BMI and obesity were also demonstrated to significantly predict a poor response following nonsurgical periodontal therapy.[29,30] In addition, Morita and coworkers reported a linear relationship between periodontitis progression and BMI over a 5-year follow-up period, with significant estimates even after adjusting for age, smoking status, and history of T2DM.[31] The same results were confirmed by a 40-year retrospective investigation conducted on US veterans[32] and by a Mendelian randomization analysis performed on the UK Biobank data set merged with summary-level genotype data of European descent from the Genetic Investigation of Anthropometric Traits Consortium, which tested the genome-wide associations for BMI and waist circumference.[33,34] The results corroborated the dose–response relationship between body weight and periodontitis, showing a significant increase in the odds of periodontitis for every 5 points increase in BMI (OR = 1.12; 95% CI: 1.06–1.17) and for every 12 cm increase in waist circumference (OR = 1.12; 95% CI:

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1.05–1.19).[35] Conversely, few studies have been published suggesting periodontitis to be a risk factor for obesity (i.e., a factor associated with an increased risk of developing a disease). In most of the publications, the clinical consequences of periodontitis, such as tooth loss and masticatory dysfunction, have been suggested as associated with obesity, potentially due to associated dietary changes.[36] In a recent systematic review, 12 out of the 16 included studies reported poorer mastication as associated with obesity, while five of the 12 studies found a direct relationship between the number of missing teeth and BMI; consistently, a higher number of teeth was associated with a lower waist circumference or waist-hip ratio.[37]

2.2.2 | Experimental evidence

Only a few studies have reported on the effect of periodontal treatment on obesity outcomes. Overall, periodontal treatment seems to reduce salivary resistin (adipocyte-derived hormone involved in insulin resistance and obesity development), serum leptin and adiponectin (adipocyte-derived hormones involved in metabolism and insulin sensitivity), as well as oxidative stress levels, although further investigations also evaluating the clinical outcomes of obesity should be conducted.[23,38,39] On the other hand, interventions aiming to achieve weight loss could provide an adjunctive beneficial effect to periodontal treatment since the concentration of markers of systemic inflammation tend to decrease after weight loss.[40] However, the literature is still unclear with regard to the periodontal impact of weight loss achieved either through nutrition or bariatric surgery. Indeed, in two subsequent studies, Martinez-Herrera et al. demonstrated that dietary weight loss implemented as adjunct to periodontal treatment provides significant beneficial effects in terms of clinical periodontal parameters as well as markers of systemic inflammation.[41,42] Furthermore, a recent systematic review including both animal and human studies highlighted the potential beneficial impact of a low-calorie diet in improving periodontal health.[43] On the other hand, multiple studies noted a deterioration in the periodontal status of obese participants undergoing bariatric surgery,[44,45] although evidence with this regard is still conflicting.[46]

2.3 | Bidirectional relationship between diabetes and obesity

2.3.1 | Observational evidence

In addition to the associations found with periodontitis, diabetes is also regarded as a comorbidity of obesity and their bidirectional association has been reported in a Mendelian Randomization analysis conducted on 14 prospective studies.[47] In fact, obesity and diabetes (especially T2DM) often coexist with a strong association between the two, with obesity being a significant risk factor for the onset of T2DM.[48–50] Meta-epidemiological evidence estimates that individuals with obesity have about 80% higher risk of developing diabetes when compared to normal weight subjects (RR = 3.92; 95% CI: 3.10–4.97).[51] On the other hand, T2DM may also contribute to the development of obesity through a variety of pathways.[23]

2.3.2 | Experimental evidence

The bidirectional association between diabetes and obesity is also confirmed by the numerous studies showing how the treatment of one disease can ameliorate the other, and vice versa. Prior to 2020, around 12 RCTs were published on the comparison between bariatric surgery and medical treatments in achieving glycemic control. It was reported that surgery decreased HbA1c levels between 1.8% and 3.5%, hypoglycemic medications resulted in smaller decreases (between 0.4% and 1.5%).[52] Likewise, in several RCTs, the administration of hypoglycemic medications for T2DM treatment such as metformin and glucagon-like peptide-1 receptor agonists (GLP-1), were proven to induce weight loss effectively and safely.[53–55]

The bidirectional associations found between periodontitis and T2DM, periodontitis and obesity, and T2DM and obesity were found to be independent of one another, and hence, a three-way relationship between the three diseases can be hypothesized. Specifically, obesity and T2DM often coexist within the framework of the metabolic syndrome (together also with hypertension, and high levels of triglycerides and low-density lipoproteins), whose association with periodontitis is consistent across several studies.[23,56,57]

2.4 | Mechanisms of association

2.4.1 | Biological mechanisms

In recent years, there has been increasing evidence about the biological mechanisms underpinning the associations between multimorbid periodontitis, diabetes, and obesity supporting a three-way relationship rather than independent two-way relationships. This topic has been thoroughly presented in previous articles,[23,58–60] and here an overview of the mechanisms will be provided to convey the depth as well as the clinical relevance of this potential three-way multimorbid relationship.

2.4.2 | Bidirectional mechanisms between periodontitis and diabetes

Starting from the association between periodontitis and diabetes, periodontitis can affect diabetes through some key mechanisms stemming from the systemic release of pro-inflammatory cytokines and bacterial products into the bloodstream caused by periodontitis.[61] In turn, this systemic inflammatory response (characterized mainly by increased C-reactive protein, IL-1, IL-6, etc.) can inhibit the insulin receptors and their downstream signaling, hence inducing insulin resistance. In addition, systemic inflammation may alter glucose

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homeostasis by hampering its uptake by the cells and thus increasing glucose blood levels.[62,63] On the other hand, diabetes/hyperglycemia can affect periodontitis through the formation of the advanced glycation end products (AGEs),[60,64,65] which, by binding to their receptor (RAGE), are able to stimulate the release of pro-inflammatory mediators from the immunoinflammatory and structural cells in the periodontium, thus triggering periodontal inflammatory and destructive processes.[60,64] Moreover, AGEs can further cause periodontal damage by promoting cross-linking of collagen (thus hampering the turnover of periodontal connective tissues cells) and by stimulating the apoptosis of osteoblastic cells (hence contributing to periodontal bone loss).[60,64] Diabetes can also lead to dysfunction of the immune cells (e.g., by reducing the chemotaxis and phagocytosis of neutrophils), which can facilitate microbial invasion and amplify the inflammatory and destructive processes within the periodontal tissues.[66–68]

2.4.3 | Bidirectional mechanisms between periodontitis and obesity

Obesity can affect periodontitis through a variety of pathways, among which the induction or increase in systemic inflammation is the primary association. The adipose tissue can potentially release several inflammatory mediators, such as adipokines (e.g., visfatin, leptin, resistin, and adiponectin), which regulate several functions, including insulin sensitivity and inflammatory and wound-healing processes.[69,70] Obesity induces a state of low-grade systemic inflammation by increasing the production of pro-inflammatory adipokines and reducing the production of anti-inflammatory mediators, such as visfatin, leptin, and resistin.[71] There is evidence that the systemic inflammatory response induced by obesity is also reflected in the periodontium as an increased concentration of pro-inflammatory markers (e.g., IL-1, IL-6, TNF-alfa, etc.) was found in the gingival crevicular fluid of obese subjects (vs normal weight).[72,73] The imbalance in the production between pro- and anti-inflammatory mediators may also lead to an altered immune response against periodontal pathogens, which can result in increased susceptibility to periodontitis.[74–76] Furthermore, obesity can also affect periodontitis via the mechanisms of insulin resistance,[71] alteration of gingival blood supply and microcirculation,[77] as well as overgrowth of specific microbial pathogens.[78,79] Conversely, the evidence on the biological mechanisms with which periodontitis can affect obesity are still largely unknown. However, some studies hypothesized that periodontitis may increase the risk of obesity through insulin resistance (induced by systemic inflammation), which in turn induces an excessive secretion of insulin, consistent with previous evidence showing higher insulin levels in subjects with periodontitis (vs no periodontitis).[80] As an anabolic hormone, insulinemia, and therefore hyperinsulinemia, may promote obesity via an increase in fat storage and glucose uptake.[81] Simultaneously, periodontitis subjects have been found to have higher serum concentrations of appetite-inducing hormones, such as ghrelin; hence, periodontitis may stimulate appetite via elevated concentrations of ghrelin.[82] The impact of periodontitis on glucoregulatory hormone levels was also demonstrated in a cross sectional study conducted on 110 severely obese, nondiabetic individuals; results showed that periodontitis was associated with impaired incretin axis, which is responsible for glucose concentrations, appetite, and body weight.[83] Ultimately, the compromised masticatory function potentially caused by periodontitis (due to tooth mobility and tooth loss) may render individuals more prone to opt for more palatable, soft, high-fat/high-calorie dietary patterns, which tend to promote obesity.[84,85]

2.4.4 | Bidirectional relationship between diabetes and obesity

The biological mechanisms linking obesity and diabetes have been largely established. Obesity can promote diabetes development and progression through a variety of pathways, including systemic inflammation and adipose tissue dysfunction (which in turn trigger the production of inflammatory mediators and adipokines inducing insulin resistance and beta-cell dysfunction), and lipotoxicity (due to the excessive storage of triglycerides in the adipose tissue, toxic lipid metabolites can accumulate and thus interfere with insulin signaling pathways).[86,87] Unsurprisingly, diabetes can affect obesity through similar mechanisms of insulin resistance and metabolic imbalance (leading to high levels of glucose and lipid in the bloodstream which promote fat storage, and to impaired glucose and energy utilization), hormonal imbalance (diabetes can affect the signaling of hormones involved in appetite control, such as leptin and ghrelin), as well as the use of specific medications that can increase appetite or enhance fat storage (e.g., insulin).[88,89]

2.5 | Shared risk factors

In addition to the abovementioned shared biological mechanisms that fuel this three-way relationship, periodontitis, diabetes, and obesity share several risk factors, which contribute to the likelihood of an individual developing the three diseases over the lifespan within a multimorbid framework.

Certain genetic variations related to immune response, metabolism, and inflammation have been shown to act on the common biological pathways shared among these three diseases, hence, although to date there is little evidence with this regard, this hypothesis is feasible. Two Mendelian Randomization (MR) studies investigated the genome-wide association between periodontitis and diabetes/hyperglycemia, but while one study only[90] found a significant higher risk of periodontitis in individuals with hyperglycemia, the other one did not support the causal relationship between the two diseases in either direction.[91] Similarly for the association between periodontitis and obesity, results from MR studies demonstrated a potential causal association of genetic liability to obesity with the risk of periodontal diseases, but no causal association was noted on the opposite direction.[35,92] Along the same lines, several genome-wide association studies acknowledged obesity, high BMI, as well as high abdominal adiposity as one of the main causal risk factors for T2DM development.[93–96]

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Numerous lifestyle factors such as tobacco use, poor nutrition, excessive alcohol consumption, and lack of regular physical exercise or a sedentary lifestyle have been shown to influence systemic inflammation and therefore chronic disease prevention and management.[89,97] These factors rely on patient engagement and self-management and can ultimately significantly affect the efficacy of medical interventions.[98] Socioeconomic position represents another relevant common risk factor among the three diseases. As opposed to genetic/epigenetic susceptibility, a low socioeconomic position has been acknowledged as a risk factor for periodontitis, diabetes, and obesity in several studies.[99,100] Furthermore, insufficient health awareness and the impact of health inequalities, conducive to unhealthy lifestyles and poor oral hygiene, have been widely recognized as a relevant risk factor for periodontitis, diabetes, and obesity.

Overall, the highlighted bidirectional relationships between periodontitis, diabetes, and obesity point toward the existence of a multimorbid three-way relationship among the three diseases. From a biological standpoint, this interplay is sustained by shared biological mechanisms such as systemic inflammation, insulin resistance, and metabolic dysfunction, while from an environmental standpoint, the three diseases share several lifestyle-related risk factors (Figure 1). Hence, the notion arises that common approaches to tackle multimorbid periodontitis, diabetes, and obesity might be beneficial.

3 | LIFESTYLES AND THE INTERPLAY BETWEEN PERIODONTITIS, DIABETES, AND OBESITY

Unhealthy lifestyles, such as poor nutrition, physical inactivity, alcohol/tobacco use, poor sleep quality, and high psychological stress, are at the root of the global burden of NCDs and constitute the multiple determinants of "health" together with genetics, environment, and access to medical care, as defined by the U.S. Department of Health and Human Services.[101] As mentioned above, the prevalence of NCDs is rapidly increasing worldwide, with their multimorbid occurrence becoming an urgent global health challenge. Hence, one of the primary aims of the "4th High-level Meeting of the United Nations General Assembly on the Prevention and Control of NCDs (2025)," an initiative of the World Health Organization (WHO), is to implement policies directed at drastically reducing exposure of individuals and populations to the common modifiable risk factors for NCDs, such as poor nutrition, physical inactivity, tobacco, or excessive alcohol use.[102] Indeed, over the last few years, national and international organizations have directed substantial attention and efforts toward the management of modifiable risk factors to prevent and manage NCDs.

In this context, the facilitation of lifestyle behavioral changes has increasingly been incorporated as a goal by many health-care professionals, ultimately resulting in a new discipline or medical specialty, the so-called "Lifestyle Medicine," gradually starting to spread across Europe. The main objective of Lifestyle Medicine (LM) is to "assist individuals and families to adopt and sustain behaviours that can improve health and quality of life."[103] In particular, the aim of this new discipline of medicine is to integrate evidence-based lifestyle practices into the modern practice of medicine with the aim to either prevent the onset of a chronic disease (by eliminating or reducing modifiable risk factors), or in case the disease is already present, to slow down its progression and facilitate its management by serving as an adjunct to the standard therapy, blending the need for both medical and patient self-care.[104] The practice of Lifestyle Medicine follows six pillars, as outlined by the British Society of Lifestyle Medicine as well as the American College of Lifestyle Medicine: good nutrition, physical activity, avoidance of toxic substances (e.g., alcohol, tobacco), low sleep disturbances, good stress management, social connections,

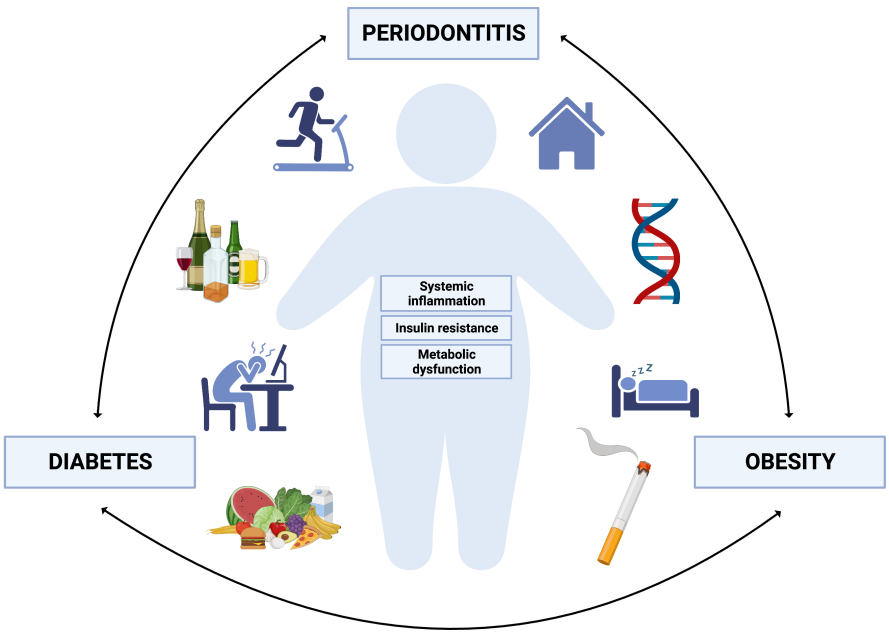

FIGURE 1 Risk factors (i.e., physical inactivity, poor nutrition, stress, poor sleep quality, alcohol/tobacco consumption, low socioeconomic status, and genetic variations) fueling the interplay between periodontitis and metabolic diseases (diabetes and obesity; figure created with BioRender.com).

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and acceptable health equity (e.g., in terms of access to healthy foods, and safe outdoor spaces for physical exercise).[105,106] Therefore, the underlying concept is that lifestyle should be looked at in a comprehensive way and should be considered a result of multiple, and closely intertwined behaviors that act synergistically with medical interventions toward health or disease.

There is a strong body of evidence that engaging in healthy lifestyle behaviors reduces the risk, or alleviates the burden, of diabetes and obesity. In this regard, evidence about periodontal diseases is promising, yet still in its infancy. Interestingly, despite the substantial mass of evidence supporting lifestyle behavioral changes, the prevalence of periodontitis, diabetes, and obesity has climbed significantly over the last decades[107] notwithstanding the numerous population-wide interventions (including behavioral as well as medical treatments) carried out to tackle the three diseases.[3] One concerning possibility behind these trends is that they may reflect the recent changes in the burden of major lifestyle-related risk factors. Indeed, over the past few decades, the advent of automation has led to the spread of the "modern lifestyle," characterized by a combination of interwoven unhealthy behaviors such as long sitting hours and physical inactivity, increased stress associated with increased virtual connectivity, poor sleep quality due to stress and excessive screen time, and poor nutrition resulting from the high consumption of ultra-processed foods, among others.[8–10] In turn, individuals adhering to patterns of unhealthy lifestyle behaviors may also be less likely to engage in regular brushing and flossing and hence be unmotivated to maintain good oral health.[108,109] Consequently, the hypothesis remains that this vicious cycle of unhealthy behaviors could increase the risk and accelerate the progression of periodontitis, diabetes, and obesity through direct and indirect mechanisms, and thus each disease can facilitate the other via shared inflammatory pathways, eventually leading to multimorbidity.[23,59] It is within this new "pandemic" of multimorbid chronic diseases that a comprehensive and systematic approach to lifestyle modifications, also encompassing the promotion of oral health, is proposed to tackle the interplay between periodontitis, diabetes, and obesity.

3.1 | Combined lifestyles and periodontitis

3.1.1 | Evidence of association

Despite the growing body of evidence on the association between each lifestyle factor and periodontal diseases (e.g., smoking, diet, physical inactivity, etc.), few studies have investigated such association considering different combinations of lifestyles as exposure.

Iwasaki and coworkers were among the first to publish evidence of the longitudinal association between combined healthy lifestyle factors and periodontitis incidence and progression in a population of 374 older Japanese adults.[87] Over 6 years follow-up, participants engaging in a combination of four healthy lifestyle behaviors (namely nonsmoking, regular physical exercise, healthy body weight, and high diet quality) were approximately 20% less likely to develop periodontitis and 30% less likely to lose teeth from periodontal causes (after adjusting for various factors including regular dental care, brushing frequency, and use of interdental cleaning devices among others), when compared to participants engaging in one or none of the listed healthy behaviors. Furthermore, a recent University-based cross sectional study examined the combined effect of adherence to Mediterranean Diet (MD) and physical activity on the periodontal status of 235 adult individuals.[110] The combination of low adherence to MD and physical inactivity led to a sixfold increase (OR = 6.4; 95% CI: 2.9–13.9) in the odds of having severe periodontitis (stage III/IV) when compared to subjects with high adherence to MD and high physical activity (PA), even after adjusting for age, gender, smoking status, and brushing frequency. Indeed, the estimate for the combined effect of MD and PA is stronger than the estimates obtained for each lifestyle factor alone, although the impact of MD seems to be more prominent than the one achieved by PA. This may have been due to the lack of discrimination between leisure time and occupational PA, which showed divergent effects on periodontitis.[111] From the previous study, a subset of 120 participants affected by Stage II/III periodontitis and with at least 20 remaining teeth were selected for therapy. Participants underwent supra- and subgingival instrumentation (i.e., Steps 1 and 2 of periodontal therapy) and they were then reassessed at 3 months to evaluate whether different unhealthy lifestyle behaviors, alone and in combination, may have affected the clinical periodontal outcomes after nonsurgical periodontal treatment.[112] After controlling for confounders (smoking, alcohol, body mass index [BMI], diabetes, and full-mouth plaque score), participants engaging in a combination of lifestyles characterized by low MD adherence, physical inactivity, high stress, and poor sleep quality resulted to be almost 50% less likely to achieve the end point of therapy (i.e., no sites with PPD ≥4 mm with bleeding on probing, and no sites with PPD ≥6 mm) after 3 months (OR = 0.9; 95% CI: 0.3–0.9). They also showed significantly higher proportions of residual sites with probing pocket depth of 6 or more.[112,113]

The available evidence on the association between lifestyles and periodontitis underlines that participants' adherence to specific combinations of healthy lifestyles may lower the risk of disease onset and progression, as well as ameliorate the response to periodontal therapy. Although healthy lifestyles and good oral health behavior tend to be clustered,[109] the reported estimates of association were obtained after adjusting for oral hygiene habits, thus an independent positive effect of healthy lifestyles on the periodontium can be hypothesized.

3.1.2 | Lifestyle interventions for the prevention and treatment of periodontitis

Research on the efficacy of lifestyle interventions for the prevention and treatment of periodontitis is still in its infancy. Although

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no specific combined lifestyle intervention-based programs have been laid out for the prevention and management of periodontitis, some studies have recently been published on the effect of lifestyle changes on clinical periodontal parameters.[114–116] A recent systematic review with meta-analysis revealed that smoking cessation was able to reduce the risk of periodontitis and make it equal to that of nonsmokers. Moreover, smoking cessation was also associated with a better response to nonsurgical periodontal therapy in terms of clinical attachment gain and pocket depth reduction.[114] Only two studies examined the effect of physical exercise behavior change interventions on periodontal parameters, and although they encompassed two different interventions (comprehensive yogi interventions vs physical exercises), they consistently showed a significant improvement in bleeding scores and probing depths after 12 weeks.[115,116] Similarly, a recent systematic review summarized the available evidence on the impact of dietary interventions in patients with periodontitis.[19] A variety of interventions were performed in the seven included studies, ranging between the implementation of a wholesome nutrition, a high-fiber and low-fat diet, a fruit and nut rich diet, or a sugar and carbohydrates poor diet with results demonstrating a significant improvement in periodontal parameters following the dietary interventions.[19] Similarly, interventions aimed at weight loss resulted in the amelioration of clinical periodontal parameters, such as bleeding scores, probing depths, and clinical attachment level.[19]

Despite the association between lifestyles and periodontitis being consistent across studies, the lack of data about the effectiveness of lifestyles interventions on periodontitis still hampers their implementation in daily clinical practice. In fact, although the latest treatment guidelines for Stage I-III periodontitis of the European Federation of Periodontology could neither recommend nor suggest the administration of lifestyle interventions (aside from smoking cessation counseling) during the Step 1 of periodontal therapy, their implementation may be encouraged as those interventions may concomitantly improve the management of other comorbidities, such as diabetes and obesity.[12]

3.2 | Combined lifestyles, diabetes, and obesity

3.2.1 | Evidence of association

Contrary to periodontitis, the epidemiological association between combined lifestyles and T2DM has been investigated more extensively. One of the first landmark studies was published by Hu and coworkers in 2001[113] and was performed on 84 941 healthy female nurses.[117] Over a 16-year follow-up, participants adhering to a combination of five healthy lifestyles (diet rich in fibers, and low in trans-fat and glycemic load, at least 30 min daily of physical exercise, no smoking, and low to no alcohol consumption) showed a 91% reduction in the risk of developing T2DM compared to subjects that did not follow the same low-risk pattern (RR = 0.09; 95% CI: 0.05–0.17).[117] The same trend was also noted by more recent meta-epidemiological evidence that summarized the results of 14 cohort studies on the incidence of T2DM. The adherence to a combination of specific healthy lifestyles (high diet quality, physical activity, nonsmoking, moderate to no alcohol consumption, and ideal body weight) was associated with a 78% reduction in the risk of T2DM. This association was found to have a dose–response relationship, with a further 32% reduction in T2DM risk for every additional healthy lifestyle factor.[118]

Few studies are available reporting on association between combined lifestyles and obesity, perhaps because obesity itself, or an elevated BMI, has been usually considered as a lifestyle-related risk factor for chronic diseases, and was not identified as a disease by the American Medical Association until a decade ago.[119] However, many epidemiological investigations have recognized specific lifestyles as risk factors for excessive weight gain or obesity. In particular, the UK Foresight Programme "Tackling Obesity" project pinned down seven main clusters of risk factors that may determine the occurrence of obesity for an individual or a group.[120] These clusters include individual-related lifestyle factors (such as unhealthy eating behaviors, e.g., overeating, eating more calories than you use, consuming a diet rich in saturated fat and added sugars, physical inactivity, high psychological stress, and lack of good-quality sleep) as well as obesogenic environmental factors (such as food marketing encouraging an unhealthy eating culture, the spread of ultra-processed foods, computer-based work dominating occupations, leisure time activities mostly related to the use of technology, excessive screen time hampering good-quality sleep, and high psychosocial stress).[89] Undoubtedly, another important element to consider is the "vicious weight gain cycle," for which the initial weight gain may reduce the capacity for physical activity, increase the psychosocial stress related to body weight stigma, and then in turn high-caloric, high-fat palatable foods start to be more frequently consumed as a coping mechanism.[121,122] Thus, the lifestyle-related risk factors fuel the self-perpetuating nature of the disease.

3.2.2 | Lifestyle interventions for the prevention and treatment of diabetes and obesity

Contrary to periodontitis, many prevention programs, mainly focused on T2DM high-risk individuals and based on lifestyle interventions, have been proposed over the last two decades to tackle the global epidemic of diabetes and obesity. One of the first randomized controlled trials showing that T2DM could be prevented with lifestyle interventions was the Finnish Diabetes Prevention Study (DPS).[123,124] The study was conducted on 522 middle-aged, overweight individuals with glucose intolerance that were allocated to receive either usual care (including general dietary and physical exercise advice) or an intensive lifestyle intervention (including additional individualized dietary counseling from a nutritionist and circuit-type resistance training sessions to increase the overall amount of physical exercise). Overall, the individualized lifestyle intervention was aimed at reducing weight and fat intake and increasing the intake of dietary fiber and the frequency of physical activity.

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Over a 4-year follow-up, the cumulative incidence of diabetes was 11% in the lifestyle intervention group versus 23% in the control group. Throughout the duration of the study, lifestyle changes were directly associated with a 58% reduction in the risk of T2DM in the intervention group.[123,124] Another widely known lifestyle-based prevention program is the Diabetes Prevention Program (DPP), a randomized controlled clinical trial conducted in 27 centers across the United States.[125] The trial compared metformin at 850 mg twice per day or an individual behavioral lifestyle intervention program with a placebo. The lifestyle intervention included 16 sessions aiming to achieve 7% of weight loss through a low-fat, low-calorie diet, and 150 min per week of moderate-to-vigorous intensity leisure time physical activity. All participants were provided with reinforcements of lifestyle behavior modification via individual and group sessions through the duration of the trial. The study was performed on more than 3000 individuals who had a minimum BMI of 25 kg/m^2 and had not received a previous diagnosis of type 1 or type 2 DM. Over a 15-year follow-up, lifestyle intervention and metformin led to a reduction of diabetes incidence rates of 27% and 18%, respectively, when compared to placebo.[126] Another large-scale prevention program aimed at investigating the different effects of lifestyle interventions was the China Da Qing Diabetes Prevention Study (CDQDPS).[127] The study was performed in 33 clinics in Da Quing (China), serving 577 adults with glucose intolerance, that were randomized to administer either no intervention or one of the lifestyle intervention groups (diet or exercise or combination of both). The dietary intervention was designed to induce weight loss in overweight/obese participants and consisted of increasing the intake of vegetables and reducing simple carbohydrate and alcohol intake, while the exercise intervention aimed to increase the amount of time spent doing leisure time physical activity. Consistently with the previous study, lifestyle interventions led to reductions in the cumulative incidence of diabetes by approximately 40%–50% over a 20-year follow-up period irrespective of baseline severity of glucose intolerance measured by fasting plasma glucose.[128–130] In addition, to effectively help prevent the onset of T2DM, lifestyle interventions sustained over a period of 10 years were found to significantly decrease the need for glucose-lowering medications in participants already affected by T2DM when compared to usual care.[131]

Given that obesity is regarded as a comorbidity and major risk factor for T2DM, many of the abovementioned lifestyle interventions-based prevention programs targeted weight loss together with diabetes management/remission, as also supported by the recent position statement from the American College of Lifestyle Medicine.[132] Conversely, other prevention programs aimed to achieve weight loss in systemically healthy individuals through a variety of combinations of dietary regimes and physical exercise. Among the most widely known programs, we can acknowledge the "Look AHEAD" program, which built upon the lifestyle intervention administered in the DPP, the "POUNDS lost" program, which encompassed a combination of low-calorie diet and moderate-intensity physical exercise prescriptions, and the "CALERIE" program which, contrarily to all the previous interventions, only encompassed the prescription of a very low energy diet. Overall, the common thread of all the strategies laid out to prevent or slow down the progression of T2DM and obesity, either alone or in combination, includes a dietary prescription characterized by a restricted calory intake below the baseline caloric intake (for around 500–750 kcal) and a physical exercise prescription encouraging at least 90–175 min per week of moderate physical activity.[133]

3.3 | Biological mechanisms linking lifestyles with periodontitis, diabetes, and obesity

The biological mechanisms underpinning the epidemiological multimorbid association between lifestyles and periodontitis, diabetes, and obesity are still largely uninvestigated. Overall, the underlying mechanisms are likely to involve those of inflammation and immune function, among others. At a systemic level, evidence is consistent with regard to the beneficial impact of each lifestyles factor in reducing systemic inflammation, oxidative stress, and maintaining immune function. A cross sectional study conducted on 842 Puerto Rican adults suggested an independent inverse association between the number of reported healthy lifestyles and the serum concentration of interleukin-6 (IL-6) and tumor necrosis factor alfa (TNF-alfa) after adjusting for age, BMI, smoking, and systemic diseases such as diabetes, hypertension, and heart diseases.[134] Furthermore, adherence to healthy lifestyles, and therefore a lower grade of systemic inflammation, was also linked to an improved immune function by acting on the T-helper 1 (Th2)/ Th2 balance and on the naïve/ memory cell ratio.[135,136] Since low-grade systemic inflammation may pave the way for the onset of chronic diseases, such as periodontitis, diabetes, and obesity, it can be hypothesized that adherence to healthy lifestyles may in turn reduce the risk of these diseases.[137] Specifically, it has been previously shown that the pathways of low-grade systemic inflammation and reactive-oxygen species overproduction may negatively affect the periodontium, by rendering the subject more prone to the onset of periodontitis or to its rapid progression.[138,139]

Consistently for diabetes pathogenesis, with the increased pro-inflammatory challenges induced by unhealthy lifestyle factors, not only massive pro-inflammatory responses in many organs (i.e., at a systemic level, in pancreatic cells, and in obese adipose tissue) are triggered, but also counter-regulatory anti-inflammatory circuits are inhibited in genetically predisposed individuals. Therefore, a sustained low-grade inflammatory response including dominance of activation signals via the nuclear factor kappa beta—NFkB, mitogen-activated protein kinase—MAPK, activator protein 1—AP-1—pathways, takes place. Examples of regulatory pro-inflammatory/anti-inflammatory circuits encompass the IL-1/IL-1 receptor antagonist (IL-1 RA) and the toll-like receptor 4 (TLR4) signaling pathway. In turn, the sustained low-grade inflammatory response activates the beta cell inhibitory and apoptotic pathways, which may be conducive to beta cell failure and insulin resistance especially if the beta cell functional and repair capacity was already compromised.[140–142]

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As for obesity, lifestyle factors such as excessive food energy intake and physical inactivity exert a direct impact on adipose tissue accumulation. Furthermore, stress was shown to contribute to obesity through a variety of pathways, including the increased resistance to leptin (appetite-suppressing hormone), the increased levels of ghrelin (appetite-stimulating hormone), and the activation of the hypothalamic–pituitary–adrenal axis (leading to an excessive cortisol secretion, which in turn reduces brain sensitivity to the leptin and promotes fat deposition in the abdominal region).[143–146] In addition, high stress levels were shown to lead to sleep disruption, which can together foster food reward processes, characterized by the frequent consumption of palatable foods that are high in calories, fat, and sugars; thus, stress and poor sleep quality can fuel unhealthy eating habits and sedentary behaviors.[147,148]

Unhealthy lifestyles are at the center of the interplay among multimorbid periodontitis, diabetes, and obesity as they act on their shared common pathogenetic pathways. Given the central role of unhealthy lifestyles in the onset, progression, and response to treatment of the three diseases, their modification toward the achievement of healthy lifestyles could be critical in successfully tackling multimorbid periodontitis and metabolic diseases (diabetes and obesity).

4 | CLINICAL IMPLEMENTATIONS

From the available evidence, it is clear how interventions aiming to change lifestyle behaviors, either independently or combined, led to the amelioration of the clinical parameters of periodontitis, diabetes, and obesity as they acted on their main pathogenetic mechanisms (i.e., systemic inflammation, insulin resistance, and metabolic dysfunction). In turn, results from interventional studies mentioned above highlighted that the specific treatment of one of the three diseases may potentially improve the management of the other two diseases—and vice versa. On these premises, the implementation of a common risk factor approach addressing the lifestyle-related risk factors common to periodontitis, diabetes, and obesity should be fostered to successfully manage the interplay among these three multimorbid diseases. Hence, the interdisciplinary approach among dental and medical professionals could be implemented to tackle multimorbidity in terms of screening/early diagnosis and treatment, both in the dental and the medical settings. Although still in their infancy, Europe has initiated projects to successfully implement this integrated approach on a large scale; examples will be provided in the following paragraphs (Figures 2 and 3). Furthermore, an overview of new possible strategies to manage multimorbidity in both the dental and the medical settings is provided in Figure 4.

4.1 | Implementation in the dental setting

Several studies have been conducted on the efficacy of screening for the risk of medical conditions, such as diabetes and obesity, in the dental setting.[149–151] The opportunistic screening for systemic conditions in the dental setting could facilitate the early detection of individuals at increased risk for a disease or, even more importantly, of those that are unaware of their increased risk. In this case, the role of dental professionals would be to then refer the patient to primary care and medical follow-up. In addition to early diagnosis/screening for medical conditions, dental professionals could contribute to the management of multimorbid periodontitis and metabolic diseases by raising awareness on their close association every time a diagnosis of periodontitis is carried out, in accordance with NHS England's "Commissioning Standard: Dental Care for People with Diabetes"[152] (Figure 2).

Another approach to tackle the interplay between periodontitis and metabolic diseases in the dental setting is by employing lifestyle behavioral changes interventions, delivered either in the form of advice or through referrals to specialists, as adjunctive to periodontal treatment. Specifically, lifestyle modifications interventions could be potentially implemented during the Step 1 of periodontal therapy, as also proposed by the latest EFP-S3 treatment guidelines for stage I-III periodontitis.[12] Therefore, dentists and oral health-care providers could play a pivotal role in fostering lifestyle behavior

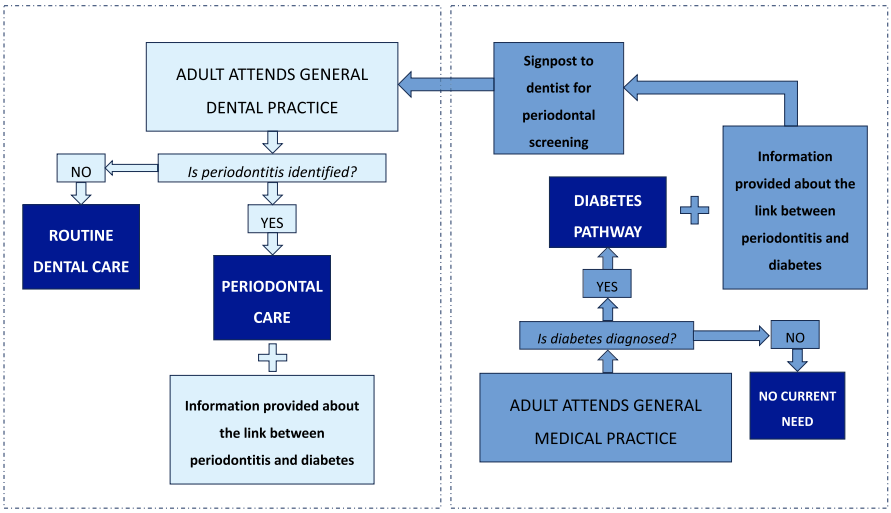

FIGURE 2 Flowchart showing the integrated care pathway for patients diagnosed with periodontitis and those diagnosed with diabetes (Figure adapted from NHS's "Commissioning Standard: Dental Care for People with Diabetes").

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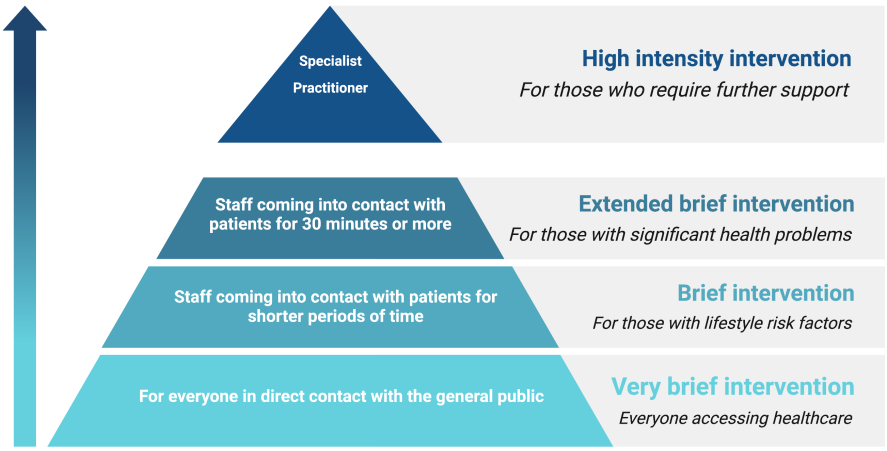

FIGURE 3 Make Every Contact Count (MECC) pyramid (Figure adapted from MECC's Consensus Statement and created with BioRender.com).

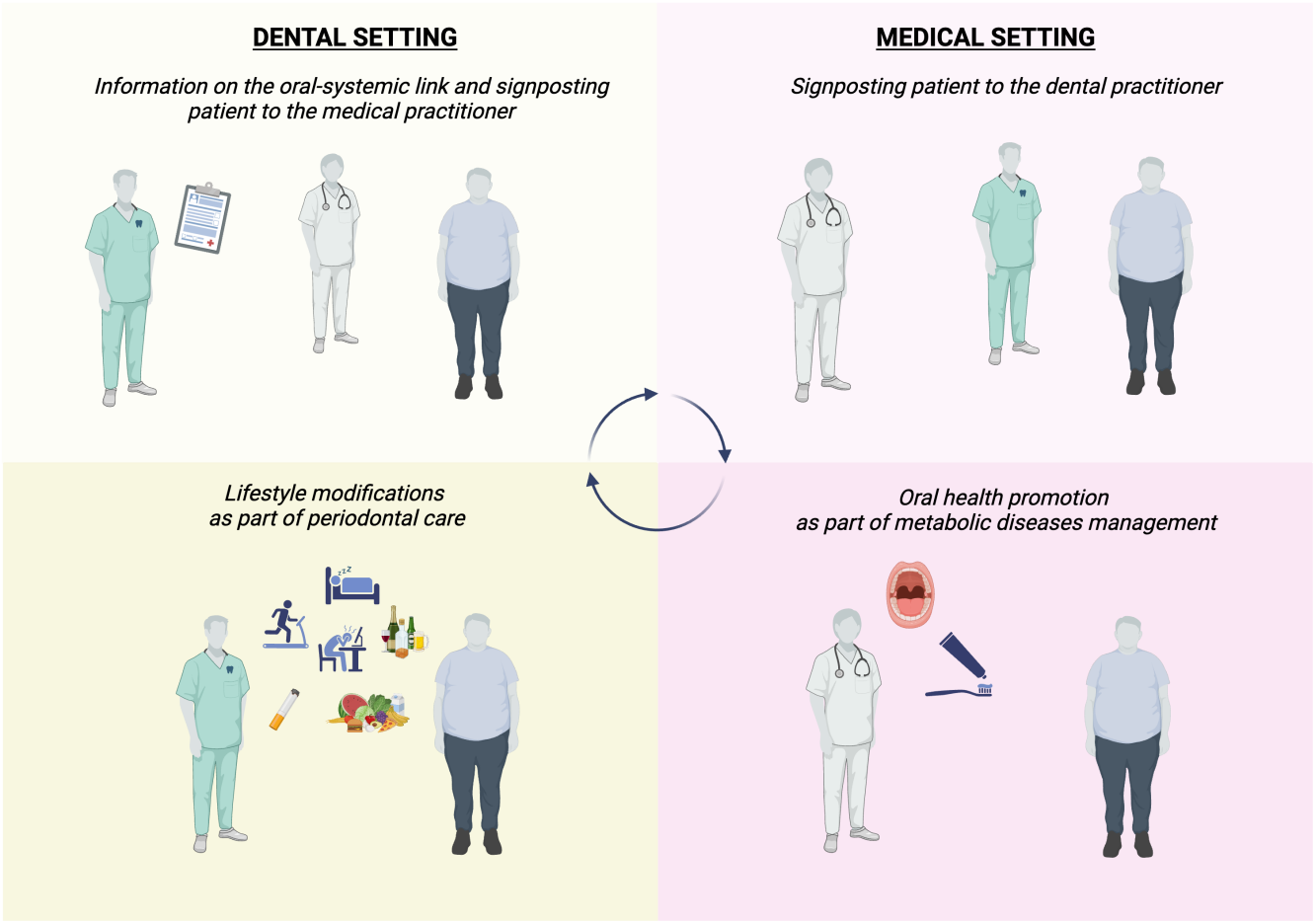

FIGURE 4 Suggested strategies to tackle multimorbidity in dental and medical settings (Figure created with BioRender.com).

changes that might not only reduce periodontal inflammation but also ameliorate glycemic control, promote weight loss, and decrease metabolic dysfunction as well as systemic inflammation, among others. Hence, although no RCTs evaluating the effectiveness of lifestyle modifications interventions as adjunctive to periodontal treatment are present, the benefits of their implementation during the Step 1 may extend beyond periodontitis, and thus be central also for the management of diabetes and obesity. Indeed, despite no cost–benefit evaluations have been performed on the approach, the systemic health benefits that can be obtained from these interventions if they are successful would represent reduced costs for the prevention and management of other comorbidities.[12,19,153,154] An example of how lifestyle modifications interventions could be delivered in the dental setting is provided by England's "Making Every Contact Count (MECC)," a project that has been laid out by Public Health England and NHS England, among others (Figure 3). MECC's goal is to facilitate behavior change by employing the millions of day-to-day interactions that organizations and individuals have with

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other people, to support them in making positive changes for their physical and mental health. MECC involves different activities that may range from signposting subjects to sources of help and support for change (e.g., apps, websites) to engaging in an oral discussion or referring for further interventions.[155]

4.2 | Implementation in the medical setting

Perhaps, a more critical part of multimorbidity prevention and management in the medical setting is the integration of oral health promotion as part of the lifestyle interventions already part of the gold standard treatment of both diabetes and obesity.[156,157] Indeed, given the systemic repercussions of periodontitis, it can be hypothesized that leaving it untreated may either reduce the effectiveness of the disease-specific treatment administered for either diabetes or obesity or, on the other hand, the reduction of periodontal inflammation achieved through oral health promotion and periodontal therapy may enhance the effectiveness of diabetes and obesity treatments. Therefore, general practitioners or medical specialists (e.g., diabetologists, cardiologists, etc.) have the possibility to integrate oral health promotion, either through patient referral to a dental care professional or by providing oral hygiene advice in addition to the promotion of other healthy lifestyles, such as diet, physical exercise, and smoking, made routinely as part of the treatment of diabetes and obesity. This joint approach between oral health-care providers and medical practitioners could be pivotal to successfully achieve lifestyle modifications, thus tackling the multimorbid occurrence of periodontitis and metabolic diseases (diabetes and obesity; Figure 4).

As mentioned above, a successful implementation of an integrated care pathway between medical and dental professionals is represented by the 2019 NHS England's Commissioning Standard. This standard provides a care pathway for those attending the general dental practice and likewise for those attending the general medical practice (Figure 2). In fact, this new clinical care pathway for patients diagnosed with diabetes aims to complement current care by raising awareness about the link between periodontitis and diabetes, and by signposting the patient to the general dental practice.[158]

5 | SUMMARY

After 30 years of investigation, with Europe occupying a central role, the multimorbid relationship between periodontitis and metabolic diseases (diabetes and obesity) is now well established based on epidemiological evidence and intervention studies with consistent results across different populations. The interplay among periodontitis, diabetes, and obesity is sustained by shared biological mechanisms, such as systemic inflammation, insulin resistance, and metabolic dysfunction, as well as common lifestyle-related risk factors. Thus, the available evidence suggests the need for a paradigm shift from a "single-disease" to a "multiple-disease" framework, characterized by an integrated multidisciplinary approach, which should include lifestyle modification interventions to successfully tackle multimorbid periodontitis and metabolic diseases. Funding for further research should be directed toward the implementation of lifestyle modifications interventions in the dental setting, as well as the integration of oral health promotion as part of the behavioral interventions routinely delivered by medical doctors for the treatment of metabolic diseases in the medical setting. Hence, a multidisciplinary integrated care pathway taking place both in the dental and medical settings and resulting from the joint efforts of dental and medical professionals should be implemented to successfully address the new global health challenge of multimorbidity.

FUNDING INFORMATION

This study was self-supported by the authors' institutions.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest in this study.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Marruganti C, Suvan JE, D'Aiuto F. Periodontitis and metabolic diseases (diabetes and obesity): Tackling multimorbidity. *Periodontol 2000*. 2023;00:1-16. doi:10.1111/prd.12536

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