Periodontal complications with obesity

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1 | CONTEXT OF THE REVIEW

In recent decades, science and technology have demonstrated profound advancements, bringing changes to society not seen since the industrial revolution. Average life expectancy has increased from 50 years of age in 1913 to 81.2 years of age in 2015, an increase of nearly 3 years per decade over the last 100 years.[1] Many infectious diseases have become almost extinct. In spite of all this, medicine continues to face unparalleled health challenges. The last century was dominated by infectious agents and discoveries of antibiotics to combat them, and now, well into the present century, the focus of medicine is on the human body's interaction with the world around us. Longer lives, together with increased understanding of biological concepts, new biomaterials, advanced diagnostic tools, and therapeutic techniques, have brought about the possibility of studying and understanding health and disease differently. More than ever before, chronic, rather than communicable, diseases present the greatest global impact on health problems; and short-term remedies are being replaced with necessarily long-term management strategies.[2] Chronic diseases, including heart disease, cancer, and respiratory and metabolic diseases, are estimated to be responsible for 60% of deaths in the world.[3] The age of noncommunicable diseases has arrived.[4] Amongst noncommunicable diseases, the growing prevalence of obesity and its complications (including type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease) are increasingly dominating global ill health and healthcare costs.

At the center of many chronic diseases is inflammation, which is both multifactorial and complex in nature. While inflammation is associated with innate and adaptive immune responses functioning beneficially to protect and heal the body, if it becomes unbalanced it can be deleterious. It is now known that inflammation occurs in different forms (acute and chronic) and that it is driven by different mechanisms of induction, regulation, and resolution. Over the last half-century a shift in the types of inflammation present in humans has occurred—from acute inflammatory responses to injury and infection, to chronic inflammatory states often related to activation of the immune system (such as in rheumatoid arthritis), with the potential mechanisms underpinning the acute inflammatory responses becoming chronic in nature.[5] Research has demonstrated the role of a number of common risk factors for noncommunicable chronic diseases, such as genetics, tobacco use, stress, alcohol consumption, physical inactivity, adiposity, and diet, in modifying immune responses and ultimately increasing mortality and the financial burden to societies.[6-8] Periodontal diseases and obesity are also risk factors implicated in the onset and progression of chronic inflammation, and its consequences. Host responses are now understood to be governed not by one factor, but by multiple factors. They manifest differently in each individual, and are further determined by the interaction of factors within and around us, thus giving momentum to shifts in medical approaches toward personalized prediction that takes account of potential modifying factors. Health has become a game of risk played out by identifying possible negative factors and then implementing strategies to balance these negative factors with positive factors, in order to attain or maintain optimal health.

Medical models of chronic disease management suggest that new paradigms are needed to address the multiplicity of factors implicated in the pathogenesis of chronic diseases and to cope with the societal demands of the continually increasing incidence of these disorders.[9-11] The shift to new systems to address the multifactorial nature of chronic diseases is strongly influenced by advances in science and technology that allow greater focus on predictive rather than reactive strategies. Increased understanding of the potential modifying factors implicated in chronic disease onset or progression has highlighted interindividual variability, particularly of those factors influenced by lifestyle.[11] This knowledge has the potential to enhance opportunities to predict, prevent, and manage chronic conditions. The personalized medicine approach requires patients to play an active part in preventing or managing their own disease; it implies an altered role for the professional, who needs to establish, with the patient, a collaborative partnership that is focused on patient participation in the decision making related to therapeutic options. Furthermore, the professional, by acting as a facilitator, can enable and empower the patient to take a central

position in driving self-management strategies. Collaborative in nature, it has been proposed that patients "will shift from being passengers to drivers of their health".[12] Research has demonstrated that interactions between patients and health professionals and the steps of patients toward healthier lifestyle behaviors are more effective if patients are engaged and active in determining their health or disease management. Patients become more skilled at self-management, ultimately gaining self-confidence and self-efficacy.[9,11,13] There are many diseases, for instance diabetes and asthma, for which this approach has reached a high level of maturity, due, in part, to the development of tools and devices that empower the patient to make day-to-day decisions about their own health management. Health promotion, described by the World Health Organization as "the process of enabling people to increase control over their health and its determinants, and thereby improve their health", through personalized medical approaches is the key to prevention and management of chronic disease.[3]

It is within this context of overall health and chronic disease, with periodontitis and obesity both categorized as noncommunicable chronic inflammatory diseases, that this review investigates and discusses periodontal complications with obesity. Since 2010, periodontitis is cited to be the sixth most prevalent chronic condition globally; obesity and overweight have now become the norm, affecting 52% of the world's population.[14] The understanding of the pathophysiology of obesity has evolved over recent decades to recognize that chronic inflammation, rather than simply mechanical burden, drives its morbidity.[15] Their common coexistence and potential synergy for driving health risks suggest that it is time to consider overweight/obesity as a modifying factor in oral health, its assessment, and management. Cardiovascular disease, one of the main complications of obesity, is also understood to be driven by the chronic inflammation associated with periodontal diseases. This meta-review summarizes aspects of existing evidence related to the possible impact of obesity on periodontal conditions.

2 | BACKGROUND

The following sections provide background understanding of the chronic inflammatory diseases periodontitis (a destructive form of periodontal diseases) and overweight/obesity (relating to obesity as a neurochemical disease). A summary of the possible associations between the two diseases is presented as a foundation to permit detailed understanding of the evidence presented in this meta-review, of the potential consequences of obesity on periodontitis and associated treatments and its relevance within the context of personalized medicine.

2.1 | Periodontal diseases

2.1.1 | Characteristics and prevalence

Periodontal diseases are chronic, multiinflammatory diseases of the periodontal tissues, propagated by an inflammatory response to bacterial plaque biofilm.[16,17] Clinical manifestations of periodontal disease include gingival inflammation (which may lead to periodontal pocket formation as a result of loss of gingival attachment), gingival recession, alveolar bone loss, tooth mobility, and eventually (if the periodontal disease is untreated) tooth loss.[18,19]

In the general population, the prevalence of periodontitis is reported to be 20%-50%.[20] Most recent estimates in the USA, based upon Centers for Disease Control and Prevention updated case definitions, suggest 47% of the adult population suffer from the disease.[21] A recent systematic review considering the global burden of severe periodontitis between 1990 and 2010 estimates the prevalence of severe periodontitis at 11.2%, placing it as the 6th most prevalent global condition.[22]

2.1.2 | Etiology and pathogenesis

Despite robust evidence about the infectious nature of periodontitis, bacteria have proven to be essential, but not sufficient, to cause disease.[23] Historically, pathogenesis was attributed to specific organisms present in larger proportions, such as Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia, serving to trigger an inflammatory response.[24] More recent information emerging from metagenomic approaches highlight the polymicrobial nature of periodontal health and disease, with the latter attributed to a dysbiotic state of the periodontal microbiota. Keystone pathogens, including P. gingivalis, could tip the balance of microbial homeostasis, leading to an altered host-microbe interaction responsible for mediating distinctive inflammatory processes associated with the loss of periodontal tissues.[25] These local acute inflammatory processes aim initially at eliminating invading organisms. A lack of mechanisms of proresolution are deemed responsible for the transition to a chronic inflammatory state.[5,24,25]

Toxic products associated with microbial shift, such as lipopolysaccharides within the gingival sulcus, may gain access to the gingival tissue and recruit a local inflammatory response characterized by neutrophils, lymphocytes, and macrophages.[26,27] Local production of proinflammatory cytokines, such as interleukin-1beta, tumor necrosis factor alpha, and interleukin-6, in order to contain/clear the insult, is, however, associated with connective tissue destruction as a result of host matrix metalloproteinase activation.[26,28,29]

A characteristic inflammatory infiltrate is observed in the periodontium; fibroblasts, junctional epithelial cells, osteoblasts/osteoclasts, macrophages, and polymorphonuclear leukocytes release proteinases that are involved in the defence against microbes.[29] At the same time, these host proteinases are capable of degrading all known extracellular components of connective tissue and epithelium, including components of both the external basal lamina (basement membrane at the connective tissue-junctional epithelium interface) and the internal basal lamina at the epithelium-tooth interface. These enzymes appear to have the potential to contribute to the lateral and apical proliferation of the junctional epithelium into the connective tissue, as well as to epithelial disintegration through degradation of the internal basal lamina and increases in epithelial permeability.

Regulation of proteinase activities involves activation of the active enzymes.[16,30]

The actual damage caused by, for example, polymorphonuclear leukocyte proteinases, may be limited in the presence of proteinase inhibitors such as alpha-2 macroglobulin, a1 antitrypsin and tissue inhibitors of metalloproteinases found in the junctional epithelium and in the gingival crevice.[31] Also, a limited proteolytic cleavage of matrix molecules and active tissue fragments may, in turn, regulate cell adhesion, migration, and proliferation in inflamed tissue.[28] Cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor alpha, and the arachidonic acid metabolite prostaglandin E_2, have been strongly associated with the onset and progression of periodontal diseases.[32] These inflammatory mediators produced within the gingival tissues are also secreted into the gingival crevicular fluid by both leukocytes and activated junctional epithelium cells, and their amounts have been shown to increase at sites exhibiting periodontal tissue destruction. They induce bone resorption and production of matrix metalloproteinase (collagenase).[33,34]

Periodontal pathogenesis is viewed as multilevel, including clinical, cellular, and subcellular mechanisms. This complex view incorporates an updated concept of modifying factors at every level, serving to facilitate further understanding of pathogenesis as new evidence emerges. More than ever before, it depicts the complexity of the biological networks that determine health and disease, highlighting the importance of understanding factors that may modify pathways, and ultimately clinical outcomes.[25,35]

2.1.3 | Risk assessment

Risk factors for a disease may be environmental, behavioral or biologic, which, if present, directly increase the probability of a disease occurring and, if absent or removed, reduce that probability. Evidence exists for the role of bacterial plaque,[36] cigarette smoking,[37,38] diabetes mellitus,[39] and HIV infection[40] as risk factors for periodontitis. The term risk indicator is used to describe a probable risk factor that has not yet been confirmed by longitudinal studies.[41] Risk indicators that may be associated with periodontitis are numerous and include age,[37] gender,[36] ethnicity,[42] socioeconomic status,[43] specific subgingival microbiota,[44] alcohol consumption,[45] interleukin-1 genotype,[46,47] inadequate physical exercise,[48] osteoporosis,[49] metabolic syndrome, obesity, and stress.[50,51]

2.2 | Overweight/obesity

2.2.1 | Characteristics

Overweight and obesity have become common terms used by the medical and scientific communities, in the press, and at social gatherings, taking on a variety of connotations and characteristics according to the context. Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health.[52] However, operational definitions use body mass index, in which overweight (body mass index ≥25 and <30 kg/m^2) and obesity (body mass index ≥30 kg/m^2) are defined (as body weight in relation to height) to lie within or above arbitrary standards.[52,53] Further explanation of body mass index as a measurement tool, and expanded World Health Organization categories, are discussed in the classification of obesity section. The body mass index thresholds were set by World Health Organization experts to represent levels of increasing health risk, with the optimal range of 21-23 kg/m^2 recommended for adult Caucasian populations.[54]

In 1998, the National Institutes of Health reported that "obesity is a complex multifactorial chronic disease",[55] followed by reference to obesity as a "chronic disease" by the World Health Organization in its report from the World Health Organization consultation on obesity in 1999.[54] Other bodies, including the American Medical Association, World Obesity Federation, and European Association for the Study of Obesity, all now recognize and classify obesity as a chronic disease.[56] While the mechanisms driving overweight and obesity are simply summarized as "an imbalance between energy intake and expenditure", the causes are more complex, involving gene-environment interactions for which the "complex feedback systems of both neural and endocrine signaling in response to intake of food", which evolved to respond to undernutrition, no longer protect the individual from overconsumption of food and subsequent weight gain.[53]

Until recently, adipose tissue was believed to be inert tissue that stored fat as a fuel depot. It is now appreciated that adipose tissue is a highly active endocrine organ secreting chemicals that drive inflammation, and that fat can also be deposited outside adipose tissue, in sites such as the liver, thus driving localized inflammation.[57] Measuring body composition to derive estimates of the total amount of adipose tissue and its distribution is therefore essential for accurately phenotyping individuals and understanding the risks of overweight and obesity.

2.2.2 | Classification

The World Health Organization definition of obesity is based on the oldest and most common measure of body composition, body mass index. Body mass index was developed by Adolphe Quatelet in 1835 during his attempts to apply statistics to explain social phenomena. One of these was to classify people's weight relative to the perceived ideal weight for their height.[53] In the early 1900s, body mass index was used by the insurance industry to demonstrate shortened lifespan, resulting in defined thresholds.[58] The World Health Organization then adopted the measure, defining a classification system; the current cut-off points are shown in Table 1.[59]

As more evidence emerges, the World Health Organization state that "health risks associated with increasing body mass index are continuous".[59] This has stimulated further breakdown of previous categories into subcategories to accommodate differing definitions of appropriate cut-off values for different ethnic backgrounds.

TABLE 1 International classification of body mass index (adapted from World Health Organization 2008[59])

Classification	Body mass index (kg/m^2)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00-16.99	16.00-16.99
Mild thinness	17.00-18.49	17.00-18.49
Normal range	18.50-24.99	18.50-22.99
		23.00-24.99
Overweight	≥25.00	≥25.00
Preobese	25.00-29.99	25.00-27.49
		27.50-29.99
Obese	≥30.00	≥30.00
Obese Class I	30.00-34.99	30.00-32.49
		32.50-34.99
Obese Class II	35.00-39.99	35.00-37.49
		37.50-39.99
Obese Class III	≥40.00	≥40.00

As other measures of body composition and shape have been incorporated, corresponding cut-off points have been proposed. Recognition of the importance of central or visceral fat in mediating the health impact of overweight and obesity[60,61] has resulted in the World Health Organization adding a threshold related to increased health risk for waist circumference (a proxy measure of central adiposity) at 94 cm for men and 80 cm for women.[59] This is a good predictor of visceral and even total body fat.[62] However, at high body mass index levels, it may be less accurate because of difficulties in obtaining an accurate measure.[63] It is generally recommended that more than one measure should be used, whenever possible, to assess body composition and fat distribution, with a selection of specific methods to be chosen based on their relevance to the health risk being assessed.[62,64]

2.2.3 | Body composition and fat distribution

While body mass index is frequently used to define overweight and obesity, it is a poor proxy for body fat.[65] Body mass index has utility as a simple, objective, and reproducible estimate of fatness in population studies; however, particularly in modestly overweight individuals, body mass index may misclassify health risks.[64] As new technologies have become available offering more accurate measurements of regional fat distribution, the appropriateness of body mass index as a measure of visceral fat in ascertaining risk associated with adiposity has been challenged.[66,67] Evidence suggests that body mass index has a very high correlation with waist circumference, waist: hip ratio, and computed tomography data regarding their association with clinical outcomes, such as diabetes incidence, and therefore body mass index remains the most commonly used measure of risk associated with central adiposity.[68,69]

In large epidemiological studies, body mass index remains predictive of health risk (cardiovascular disease, cancer, and mortality), but it can be augmented by anthropometric measures of fat distribution.[70] Body composition can be defined in several ways. Most commonly, a two-compartment model assumes that the body is composed of fat and nonfat or lean body masses. Fat can be measured directly by dual X-ray absorptiometry, computed tomography, or magnetic resonance imaging, or estimated from measurement of body water by deuterium dilution. Hydrodensitometry or air displacement can allow body volume, and thus density, to measured, and then body fat is estimated using derived equations.[71] More complex models that do not make assumptions about the hydration of lean tissue can be developed and these may be important in disease states, or where body composition changes in response to treatment, for example, type 2 diabetes.[72] As knowledge of the health risks associated with being overweight or obese has increased over the last 100 years, focus on both the fat and lean body mass components of body composition have become increasingly recognized as determining the pathological significance of body mass index. Fat levels are dynamic over a lifetime and vary according to age, gender, ethnicity, level of physical activity, and hormonal status. For example, the percentage of body fat increases with age for both men and women, and women generally have a higher percentage of body fat than men, regardless of age, from puberty onward.[73]

More recently, attention has been focused on body fat distribution rather than solely on fat mass. Visceral (intra-abdominal) fat has been shown to be more highly associated with the metabolic syndrome than subcutaneous fat, with the suggested mechanism being linked to differences in adipokine secretion.[74] Figure 1 depicts areas of fat distribution in the body. There is evidence that proinflammatory adipokines are overproduced with increasing adiposity, with their distribution selectively altering the effects on systemic inflammation.[75]
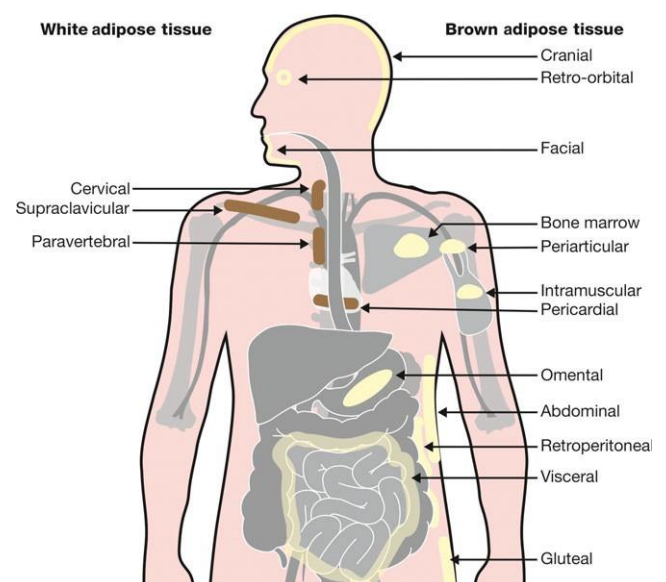

FIGURE 1 Body fat distribution

2.2.4 | Assessment

Assessment of overweight/obesity holds challenges similar to those of other chronic diseases, including periodontitis. The pursuit to define a measure that is both feasible and relevant to basic research, epidemiological research, clinical research, and most importantly, patient outcomes, is a never-ending journey.[76] However, over recent years attempts have been made to improve the staging of obesity, so that the severity of its complications is amalgamated with body mass index. The Edmonton Obesity Staging System combines a severity stage for metabolic, "mechanical", and mental health components of obesity and has been shown to improve risk assessment for mortality outcome more accurately than body mass index alone.[77,78]

There are several guidelines on clinical assessment of the obese individual, but in general these do not include measures of inflammation.[79]

2.2.5 | Prevalence

The World Health Organization reported overweight/obesity statistics as early as the 1930s and it currently maintains a Global Body Mass Index Database.[59] In 1997, it reported obesity as an emerging public health problem of epidemic proportions. The worldwide prevalence of obesity has almost tripled since 1975, with 39% of adults estimated to be obese, corresponding to 650 million individuals aged over 18 years.[52] In 2016, 41 million children under the age of 5 years, and 340 million of those aged between 5 and 19 years, were reported as overweight or obese.[52]

2.2.6 | Health risks associated with obesity

Obesity has been said to "increase morbidity and mortality through its multiple effects on nearly every human system".[80] The World Health Organization Global Observatory states that at least 2.8 million people worldwide die each year as a result of overweight or obesity, with mortality rates increasing with higher body mass index.[81] The disability-adjusted life year is a measure of overall disease burden, expressed as the number of years lost due to ill health. It is estimated that globally, 35.8 million (2.3%) disability-adjusted life years are caused by overweight or obesity.[54]

There is increasing research evidence demonstrating the association between obesity and increased risk for high blood pressure, cardiovascular disease, osteoarthritis, respiratory disorders, type 2 diabetes, reproductive dysfunction, gallbladder disease, and cancer. In addition, an association of obesity with gastrointestinal, liver, urogenital, skin, and surgical site infections has been described.[80,82,83]

To achieve optimal health, the median body mass index for an adult population should be 21-23 kg/m^2, while the goal for individuals should be to maintain body mass index between 18.5 and 24.9 kg/m^2. There is increased risk of comorbidities for body mass index 25.0-29.9 kg/m^2, and moderate-to-severe risk of comorbidities for body mass index greater than 30 kg/m^2.[52]

2.2.7 | Etiology

The etiological classification of obesity can be summarized into 5 main categories—genetic, neuroendocrine, drug-induced, sedentary lifestyle, and diet—with many complex mechanisms implicated within each category.[53,84] At the simplest level, obesity can be explained as a condition that results when energy intake exceeds energy expenditure, with imbalance provoking changes in the body's fat stores. Two underlying, currently indisputable, laws of obesity suggest that, first, for obesity to develop, energy intake must exceed energy expenditure and, second, obese individuals have a higher level of energy expenditure than lean individuals and therefore require higher energy intake to maintain their higher body mass.[85]

As simple as "energy in versus energy out" may sound, resulting in the stereotypical solution of "eat less and exercise more", the list of underlying factors that can potentially contribute to energy balance are extensive. The aforementioned etiological classification highlights the aspects that may determine energy intake or expenditure. For example, genetic, neuroendocrine and drug-induced categories may alter appetite or sensation of satiety.[86] A combination of all 5 aspects may affect an individual's capacity to maintain or increase energy expenditure.

A large number of twin, adoption, and family studies have explored the level of heritability of obesity, in other words the fraction of the population variation in a trait (eg, body mass index) that can be explained by genetic transmission.[87] Recent studies of individuals with a wide range of body mass index values, together with information obtained on their parents, siblings, and spouses, suggest that about 25%-40% of the individual differences in body mass or body fat may depend on genetic factors. However, studies with identical twins reared separately suggest that the genetic contribution to body mass index may be higher (ie, about 70%).[88] Genome-wide association studies have identified nearly 600 polymorphisms that are associated with body weight and altered appetite. Furthermore, specific mutations in key genes, such as those coding for leptin or its receptor, the melanocortin receptor, are known to lead to early childhood obesity.[89,90]

However, the recent rapid increase in the prevalence of obesity cannot be accounted for simply by genetic change, suggesting that environmental determinants are also important.[83] Environmental influences on overweight and obesity are primarily related to food intake and physical activity behaviors. In many countries where the population consumes westernized diets there is an overall abundance of palatable, calorie-dense food. In addition, aggressive and sophisticated food marketing in the mass media, supermarkets, and restaurants, and the large portions of food served outside the home, promote high calorie consumption.[91,92]

Many of our sociocultural traditions promote overeating and the preferential consumption of high-calorie foods. For many people, even when calorific intake is not above the recommended level, the number of calories expended in physical activity is insufficient to offset consumption. Many people are entrenched in sedentary daily routines consisting of sitting at work, sitting in traffic, and sitting in

front of a television or a computer monitor for most of their waking hours.[83,93]

Research relating obesity to psychological disorders and emotional distress is based on community studies and clinical studies of patients seeking treatment. Several recent studies in general populations suggest a relationship between obesity and emotional problems.[94] Similarly, overweight people undergoing weight loss treatment may, in clinical settings, exhibit signs of emotional disturbance. In a review of dieting and depression, there was a high incidence of emotional illness symptoms in outpatients treated for obesity.[94]

2.2.8 | Pathogenesis

Adipose tissue, previously viewed as a passive energy store, is now referred to as an endocrine organ in itself.[80] As adipocytes become larger, they demonstrate altered activity with increased release of proinflammatory mediators and decreased release of antiinflammatory cytokines[95,96] (Figure 2). Macrophages are recruited through signaling by chemokines (chemokine ligand 2) as a consequence of fat cell expansion and increase during weight gain. The macrophages are primarily located near apoptotic adipocytes. Various mediators synthesized by the fat cells and resident macrophages then contribute to local and systemic inflammation through increased production of interleukin-6, tumor necrosis factor alpha, and other proinflammatory cytokines.[75,95,97]

Hence, it is now known that adipose tissue is actively involved in the regulation of inflammation and immunity associated with the dysregulated or altered release of a variety of proinflammatory and anti-inflammatory factors (eg, leptin, adiponectin, cytokines, and chemokines).[80] Visceral fat (associated with central adiposity) has greater activity than peripheral fat cells regarding the production of endocrine secretions responsible for the effect of fat mass on immune function.[69,98]

The crucial role of adipose tissue in obesity-related systemic inflammation is the active production of hormones and cytokines, which acts as the link to many comorbidities of obesity.[99] Obese fat tissue (enlarged adipocytes compared with lean fat tissue), characterized by macrophage accumulation from the migration of inflammatory monocytes that infiltrate the adipose tissue from the circulation, results in secretion of tumor necrosis factor alpha and interleukin-6 by both adipocytes and macrophages. These cytokines (also classified as adipo[cyto]kines) regulate systemic inflammation, affecting insulin sensitivity and glucose metabolism (associated with chemokine signaling). Interleukin-6 is associated with decreased insulin signaling and induction of fatty acid oxidation, as well as secretion of C-reactive protein by the liver. Interleukin-6 expression and lipolysis (in the fat cells) are increased by tumor necrosis factor alpha and are known to play a role in insulin resistance.[75,97] Table 2 lists the myriad of adipokine activity playing a role in the pathogenesis of adipose tissue, and the associated diseases.[97] There is evidence that some of the anti- or proinflammatory effects of adipokines are active in the innate immune response and that others stimulate an adaptive immune response.[100]
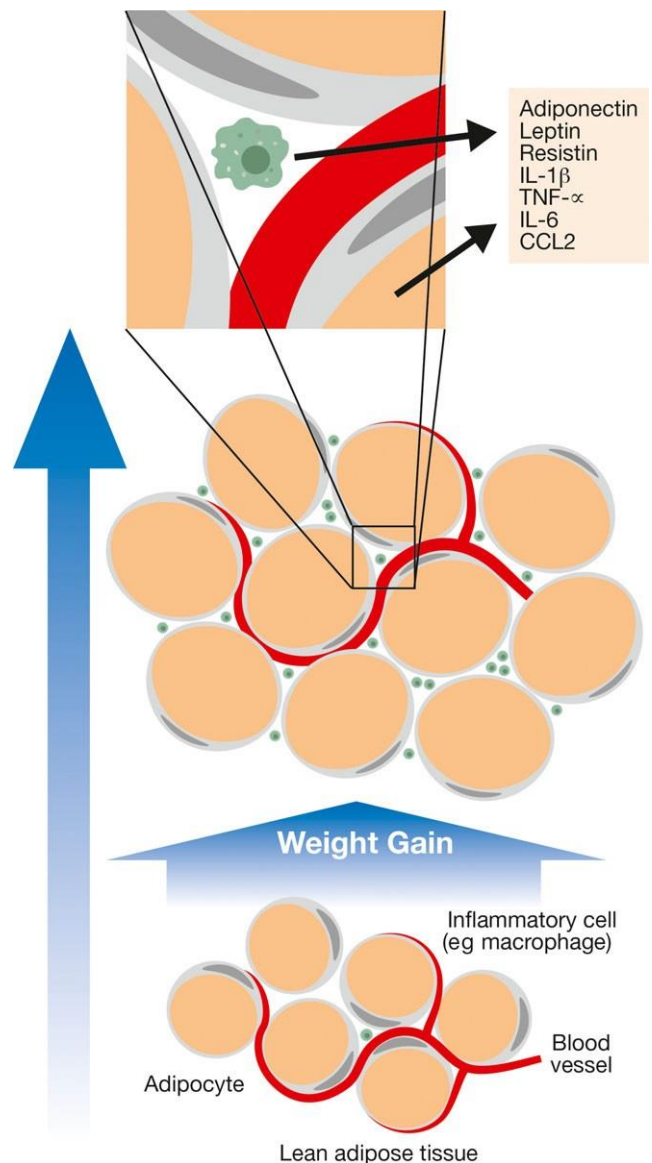

FIGURE 2 Cellular components of lean and obese adipose tissue. CCL2, C-C motif chemokine ligand 2; IL-1b, interleukin-1beta; IL-6, interleukin-6; TNF-a, tumor necrosis factor alpha

2.2.9 | Risk assessment

The World Health Organization has identified the importance of addressing common risk factors to reduce the prevalence of noncommunicable diseases, including obesity.[4,52,101] Linked to the multifactorial nature of overweight and obesity, identified risks include not only those at the individual level, but also those at a societal or environmental level. For health professionals, patient level modifiable risk factors are most relevant; however, these may be included with other, less modifiable, factors.

The most common risk factors for weight gain or obesity are tobacco cessation, consumption of foods high in saturated and trans fats, salt intake, sugar consumption (especially in sweetened drinks), sedentary lifestyle, as well as excessive alcohol consumption.[59] In

TABLE 2 Adipocytokine activity in adipose tissue pathogenesis

Adipocytokine	Inflammatory effect	Effects on innate immunity	Effects on adaptive immunity	Associated diseases
Adiponectin	Anti-inflammatory	↓Endothelial adhesion molecules ↓ NF-kB ↓ TNF ↓ IL-6 ↓ IFN-c ↑ IL-10 ↑ IL-1RA ↓ Phagocytosis	↓ B-cell lymphopoiesis ↓ T-cell responses	Insulin resistance and type 2 diabetes mellitus Atherosclerosis Experimentally induced liver disease: nonalcoholic and alcoholic fatty liver disease Cardiac injury CancerInflammatory bowel disease
	Proinflammatory	↑ CXCL8 in presence of LPS	Not determined	Rheumatoid arthritis
Leptin	Proinflammatory	↑ TNF ↑ IL-6 ↑ IL-12 ↑ Neutrophil activation (CD11b) ↑ ROS ↑ Chemotaxis ↑ NK cell function	↑ Lymphopoiesis ↑ Thymocyte survival ↑ T-cell proliferation ↑ Th-1 response (IL-2 and IFN-c) ↓ Th-2 response (IL-4)	Insulin resistance Experimentally induced hepatitis EAE and antigen-induced arthritis Experimentally induced colitis (mice) Asthma Cancer
Resistin	Proinflammatory	↑ TNF ↑ IL-1b ↑ IL-6 ↑ IL-12 ↑ NF-**j**B ↑ Endothelial adhesion molecules (VCAM1 and ICAM1)	Not determined	Insulin resistance (mice) Type 2 diabetes mellitus (mice) Rheumatoid arthritis Atherosclerosis Nonalcoholic fatty liver disease Chronic kidney disease
Visfatin	Not determined	↑ IL-6 ↑ IL-8 ↓ Apoptosis of neutrophils	Not determined	Insulin resistance and type 2 diabetes mellitus Acute lung injury Sepsis

↓, decrease; ↑, increase; CXCL, CXC-chemokine ligand; EAE, experimental autoimmune encephalomyelitis; ICAM, intercellular adhesion molecule; IFN-c, interferon-c; IL, interleukin; IL-1RA, IL-1 receptor antagonist; LPS, lipopolysaccharide; NF-kB, nuclear factor- kB; NK, natural killer; ROS, reactive oxygen species; Th-1, T-helper 1 cell; Th-2, T-helper 2 cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.
Adapted from Tilg and Moschen.[95]

addition, a number of medications are associated with weight gain. These medications include some antidepressants, antiseizure medications, diabetes medications, antipsychotic medications, steroids, and beta-blockers.[102] A systematic review of weight gain following smoking cessation has shown that individuals who quit smoking will experience greater weight gain than nonsmokers for a minimum of 1 year.[103]

Sucrose-containing drinks have been identified as a major dietary factor with a greater impact than many other types of food, partly because of the high number of calories in these products. Sugary drinks are easily and quickly consumed, and supply a large number of calories but little nutrition or sense of satiety.[104] Unhealthy diet and sedentary lifestyle are fundamental in assessing risk for overweight and obesity. Accordingly, the impact of these two factors in the etiology of obesity - energy in vs. energy out - is indisputable and they remain at the center of weight gain. However, awareness of a risk factor does not necessarily make it simple to modify. Socioeconomic and environmental factors known to affect diet and activity levels have been identified as fundamental elements affecting the risk for overweight and obesity. Education levels and health

awareness can influence food purchasing and cooking patterns. Lifestyle factors, such as watching television, eating out, working night shifts, and the distance between home and school or work, are just a few examples of confounding determinants of diet or physical activity.[55,105,106] Individuals with irregular and insufficient sleep patterns have been shown to be at a higher risk of weight gain. This is reported to be related to the link between hormone levels/neuroendocrine signaling and appetite/satiety; however, poor dietary habits associated with irregular sleep and work schedules have been implicated as a confounder in this association.[84]

2.2.10 | Therapy for obesity

Treatment of obesity aims to help the individual maintain a negative energy balance for a sufficiently long duration to utilize stored energy and thus lose weight, and then maintain a lower energy intake and/or increased energy expenditure for long-term maintenance of weight loss.[107] Treatment is problematic because there is clear evidence that physiological mechanisms try to maintain body

weight and restore lost weight, and so-called lifestyle interventions (diet and exercise) result in weight loss of only 2%-3% which is maintained beyond 1-2 years.[108] More intensive interventions, such as those deployed in the Look Action For Health In Diabetes trial, or by using low (or very low) energy diets, can produce both greater initial weight loss and longer term weight-loss maintenance.[109] Pharmacotherapies have been developed that can, in conjunction with diet and lifestyle, produce greater and more sustained weight losses of 8%-10%.[110] However, the development of (laparoscopic) bariatric surgery has shown the greatest impact on weight loss, weight-loss maintenance, and improvement in complications caused by obesity, as well as opening research areas on mechanisms for weight loss, including gut hormones, microbiota, and bile acids.[111-113] It is also increasingly recognized that the weight loss achieved, and perhaps the mechanisms involved after bariatric surgery, have marked beneficial effects on adipose tissue and systemic inflammation.[114]

2.2.11 | Obesity and periodontal diseases

Obesity has been shown to modulate the host immune response, resulting in increased susceptibility to various infections and exaggerated host immune responses to them.[80] Adipose tissue (adipocytes) secretes several proinflammatory factors, also implicated in periodontitis, including cytokines (eg, interleukin-6) and chemokines, and can affect T-cell function.[80] Thirty years ago, experimental evidence suggested a possible association between obesity and periodontitis. In 1977, Perlstein & Bissada[115] published an animal study demonstrating greater alveolar bone resorption in obese compared with nonobese rats. This is in agreement with a more recent report from Amar et al[116] that confirmed dysregulation of immune responses in a periodontitis animal model resulting in increased bone loss. Early evidence suggests that obese individuals are 2-3 times more likely to suffer from periodontitis independently of traditional risk factors (including age, gender, and cigarette smoking).[117-122] Several clinical studies investigating the association between obesity and periodontitis have been published in the last 20 years. In addition, a number of systematic reviews have been published during the last 7 years.

Personalized, preventive, and predictive medicine are dependent on robust research evidence to guide clinical assessment, diagnosis, and decision-making. Large volumes of published literature are available electronically to clinicians. However, the sheer mass of evidence can be overwhelming. Reviews serve to summarize bodies of evidence. Systematic reviews conducted according to a well-formulated question and protocol to minimize bias in the inclusion of primary studies facilitate the summary of numerous studies, thus allowing clinicians to keep abreast of current literature.[123] Furthermore, meta-analysis performed as part of systematic reviews combines results to provide an overall summary estimating the results of multiple studies.[124] In a situation in which multiple systematic reviews have been published, a meta-review proposes to summarize the content of these multiple systematic reviews, providing an optimal overview of existing evidence and gaps in the research findings.[125] Assessment of methodological quality is a key part of the process to assist readers

in determining the validity and clinical applicability of the findings to their patients or setting.[126] Therefore, the aim of this review is to summarize research evidence to date pertaining to the possible periodontal complications with obesity, using a meta-review approach.

3 | META-REVIEW METHODS

This meta-review was designed and conducted based upon the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[127,128]

3.1 | Focused question

A focused question was developed using the population, exposure, comparison, outcome criteria[129]: "What is the association of periodontal diseases and/or periodontal complications and overweight/obesity in children, adolescents, and adults?"

3.2 | Scope of the review

All systematic reviews were eligible for inclusion if they reported on research studies conducted in human subjects on the potential association or consequences of overweight/obesity and periodontal diseases in children, adolescents, or adults and were carried out according to systematic review methodology.

3.3 | Search and screening

The electronic search strategy was developed using Medical Subject Headings (MeSH) and freetext terms based on overweight/obesity and periodontal/periodontitis, then piloted to confirm its suitability to the focus of the review. In the electronic search, databases were searched to 31 October 2017 using a basic search strategy set a priori and customized as appropriate for each database (Cochrane Library, Ovid National Library of Medicine Database [MEDLINE], Excerpta Medica database [EMBASE], and Literatura Latino-Americana e do Caribe em Ciências da Saúde [LILACS]). English language was applied as a restriction. Manual searching consisted of checking bibliographic references of review articles. Figure 3 provides an example of the basic search strategy.

Search results were combined in one database and duplicates were removed. Titles and abstracts (when available) of all reports identified through the search were screened by one reviewer (JES) for reviews appearing to meet the inclusion criteria. Full text articles were obtained for potentially relevant reviews, which were then further screened by two reviewers (JES and FD) to confirm their eligibility for inclusion. Narrative reviews or nonrelevant reviews were excluded.

3.4 | Risk of bias assessment and data abstraction

Assessment of the quality of included systematic reviews was performed according to A MeaSurement Tool to Assess systematic

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1. PERIODONTAL DISEASES.mp.
2. periodont$.mp.
3. gingiv$.mp.
4. (gingiv$ adj health).mp.
5. (ging$ adj disease).mp.
6. (inflamm$ adj gingiv$).mp.
7. GINGIVITIS.mp.
8. Human.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7
10. 8 and 9
11. OBESITY.mp.
12. Obes$.mp.
13. Body weight.mp.
14. Body composition.mp.
15. Body fat.mp.
16. hyperphagia.mp.
17. adipos$.mp.
18. overweight.mp.
19. over weight.mp.
20. overeat.mp.
21. overfeed.mp.
22. binge eating disorder.mp.
23. weight gain.mp.
24. weight loss.mp.
25. fat overload syndrome.mp.
26. body mass index.mp.
27. waist circumference.mp.
28. waist hip.mp.
29. (weight adj over).mp.
30. (weight adj reduc$).mp.
31. (weight adj reduc$).mp.
32. (weight adj loss).mp.
33. (weight adj maint$).mp.
34. (weight adj decreas$).mp.
35. (weight adj watch$).mp.
36. (weight adj control).mp.
37. diet.mp.
38. body weight measure.mp. [mp = ti, ot, ab, nm, hw]
39. BMI.mp.
40. metabol$.mp.
41. metabolic syndrome.mp.
42. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or
    22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or
    33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. 8 and 42
44. 10 and 43
45. 44 and Systematic Review
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FIGURE 3 Search strategy example for Ovid MEDLINE

Reviews (AMSTAR).[123] Electronically generated evidence table templates were used for abstracting data from the full text articles (JS). Evidence tables were quality checked for accuracy following data abstraction (FD).

4 | RESULTS

4.1 | Study selection

Electronic searches resulted in a total of 486 titles and abstracts, with 9 articles identified through checking of bibliographic lists, resulting in 342 being screened for eligibility following elimination of duplicates. Twenty-eight full text articles were screened for systematic reviews investigating the association of overweight/obesity and periodontal diseases. Following exclusion of narrative reviews or nonrelevant reviews, 14 full text systematic reviews were deemed eligible for inclusion in the meta-review.[130-143] Figure 4 depicts the Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram summarizing the search and screening process.

Eleven of the 14 systematic reviews included were published between 2015 and 2017 with the remaining 3 being published between 2010 and 2014. Six reviews included only cross-sectional or longitudinal studies, while 8 reviews included only longitudinal or experimental studies. Two of the 14 reviews reported on children or adolescents only and 2 included adolescents with adult population samples. Table 3 provides an overview of the systematic reviews included, Figure 5 depicts the breakdown of study designs, and Figure 6 shows the proportion of studies providing evidence of an association between overweight/obesity and periodontal diseases.

Table 4 summarizes the characteristics and results of the systematic reviews. Based on A MeaSurement Tool to Assess systematic Reviews (AMSTAR) for the bias assessment of systematic reviews, the majority of the included reviews were deemed to be of moderate-to-high quality (Table 5).

The systematic reviews included focused on 4 main themes of association: overweight/obesity and periodontitis prevalence (some reporting extent and severity); incidence; response to periodontal therapy; and/or periodontal disease biomarkers. The 14 reviews contained some overlap of articles but only 2 included exactly the same articles. Overall, the 14 systematic reviews included a total of 133 unique study publications. Reviews published earlier included a larger number of observational studies, while more recent reviews included longitudinal and experimental studies.

4.2 | Overweight/obesity and periodontitis prevalence

Nine systematic reviews reported on the prevalence or extent and severity of periodontal complications in overweight or obese individuals.[131,132,134,135,136,137,138,139,143] Two of these reviews included studies solely of children and adolescents.[135,136] Data from these 9 reviews show that obese individuals are more likely to have a form of periodontal disease than normal weight individuals, independent of age or gender. In addition, increasing levels of overweight through obesity are associated with more extensive and severe periodontitis.

4.3 | Overweight/obese and periodontitis incidence or progression

Four systematic reviews were identified that report on the incidence of periodontal diseases or progression in overweight/obese or cases of weight gain, with 2 including studies investigating children or adolescents.[134,136,141,143] These summaries of longitudinal studies show that overweight/obesity or weight gain increases the risk of onset and/or progression of periodontal diseases.

4.4 | Overweight/obese and response to periodontal therapy

Six systematic reviews reported the potential effect of obesity on the clinical response to nonsurgical periodontal
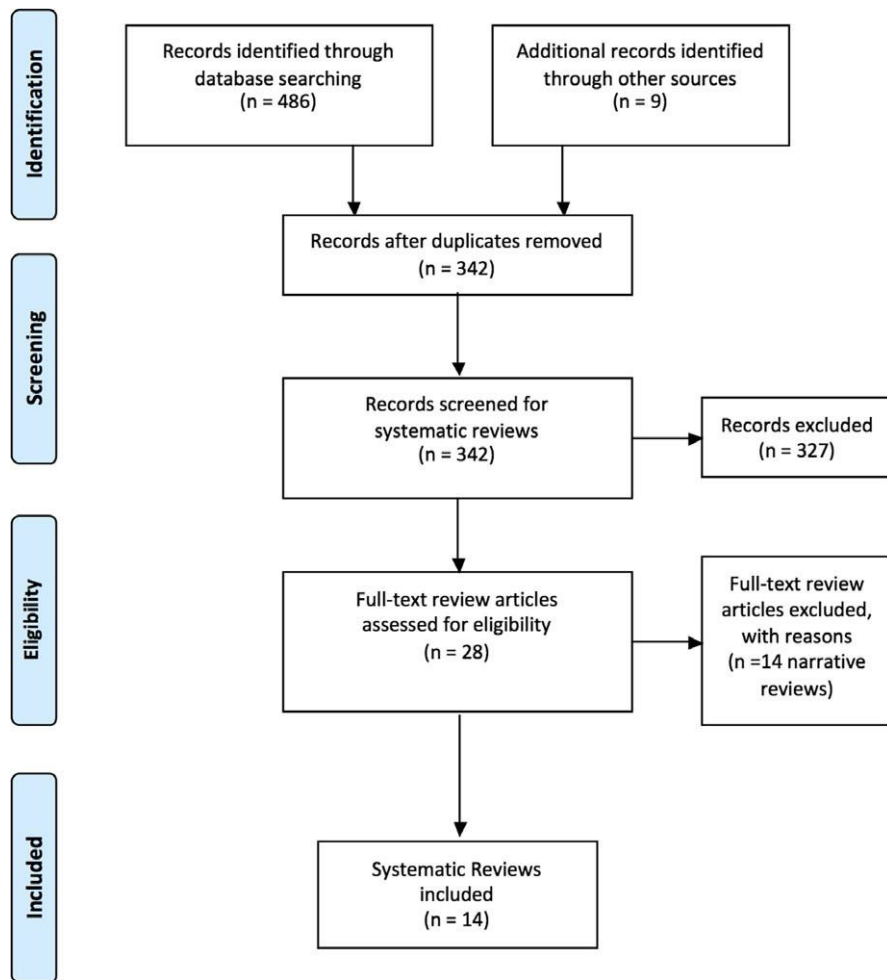
FIGURE 4 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

therapy.[131,133,134,137,140,142] Two of these reviews included the same 5 studies. Overall, 5 reviews reported inconsistent evidence of differing clinical responses to nonsurgical periodontal therapy in obese individuals. One review reported evidence of obesity as a factor associated with a poorer response to nonsurgical periodontal therapy. All reviews reported the limited number of studies with small sample size and high levels of heterogeneity in design as restrictions to forming conclusive statements on the effect of obesity on healing following periodontal therapy.

4.5 | Overweight/obesity and biomarkers

Five systematic reviews reported on prevalence or change in biomarkers associated with inflammation, periodontitis, or obesity.[130,131,137,140,142] One review reported 2 studies demonstrating increased levels of tumor necrosis factor alpha and decreased levels of adiponectin in obese subjects, with a reduction of tumor necrosis factor alpha and increase in adiponectin following treatment.[142] However, it was noted that these results were not consistent across studies. The levels of C-reactive protein and proinflammatory cytokines tended to be higher in obese subjects than in nonobese subjects

and showed a positive correlation to body mass index. Reduction of cytokine levels following periodontal treatment was reported in some studies but was inconsistent across studies. Each of the reviews reported inconsistency in results of the levels of serum cytokines in obese individuals and the potential effect of confounding factors.

4.6 | Overweight/obese and periodontal status in children/adolescents

Two reviews reported on studies of periodontal conditions, such as gingivitis and/or biomarkers of inflammation, in children or adolescents.[135,136] These reviews reported poorer gingival health in obese subjects compared with nonobese subjects with an odds ratio of 1.46 (95% confidence interval: 1.20-1.77) for periodontitis and obesity, and an odds ratio of 5.41 (95% CI: 2.75-10.63) for bleeding on probing and obesity. Plaque levels were reported to be higher, and dietary choices poorer, than in obese and in nonobese children/adolescents; however, associations were independent of these factors.

TABLE 3 Overview of included systematic reviews

Systematic review characteristic	Number of reviews (n = 14)	Author year (reference number)·
Publication year		
Published prior to and including 2014	3	Chaffee and Weston (2010)[132]
		Moura-Grec et al (2014)[138]
		Suvan et al (2011)[143]
Published 2015-2017	11	Akram et al (2016)[130,131]
		Gerber et al (2016)[133]
		Keller et al (2015)[134]
		Li et al (2015)[135]
		Martens et al (2017)[136]
		Martinez-Herrera et al (2017)[137]
		Nascimento et al (2016)[139,140]
		Nascimento et al (2015)[141]
		Papageorgiou et al (2015)[142]
Country of corresponding author		
Belgium	1	Martens et al (2017)[136]
Brazil	4	Moura-Grec et al (2014)[138]
		Nascimento et al (2016)[139,140]
		Nascimento et al (2015)[141]
Denmark	1	Keller et al (2015)[134]
Germany	1	Papageorgiou et al (2015)[142]
Hong Kong	1	Li et al (2015)[135]
Malaysia	2	Akram et al (2016)[130,131]
Spain	1	Martinez-Herrera et al (2017)[137]
Switzerland	1	Gerber et al (2016)[133]
UK	1	Suvan et al (2011)[143]
USA	1	Chaffee and Weston (2010)[132]
Design of included studies		
Cross-sectional only	3	Li et al (2015)[135]
		Moura-Grec et al (2014)[138]
		Nascimento et al (2016)[139]
Cross-sectional and longitudinal	3	Chaffee and Weston (2010)[132]
		Martens et al (2017)[136]
		Suvan et al (2011)[143]
Cross-sectional and experimental	2	Akram et al (2016)[130]
		Martinez-Herrera et al (2017)[137]
Longitudinal only	1	Nascimento et al (2015)[141]

(Continues)

TABLE 3 (Continued)

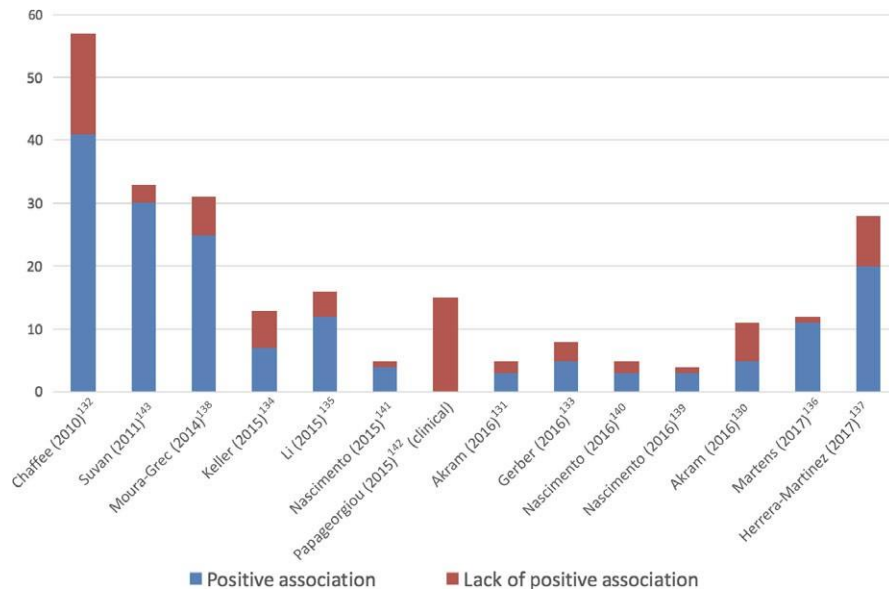| Systematic review characteristic	Number of reviews (n = 14)	Author year (reference number)·
Longitudinal and experimental	1	Keller et al (2015)[134]
Experimental only	4	Akram et al (2016)[131]
		Gerber et al (2016)[133]
		Nascimento et al (2016)[140]
		Papageorgiou et al (2015)[142]
Population sample		
Adult only	10	Akram et al (2016)[131]
		Chaffee and Weston (2010)[132]
		Gerber et al (2016)[133]
		Keller et al (2015)[134]
		Martinez-Herrera et al (2017)[137]
		Nascimento et al (2016)[139,140]
		Nascimento et al (2015)[141]
		Papageorgiou et al (2015)[142]
		Suvan et al (2011)[143]
Children/adolescent	2	Li et al (2015)[135]
		Martens et al (2017)[136]
Adult and adolescent	2	Akram et al (2016)
		Moura-Grec et al (2014)[138]
Interventions treatment response studies		
Nonsurgical only	4	Akram et al (2016)[131]
		Keller et al (2015)[134]
		Martinez-Herrera et al (2017)[137]
		Nascimento (2016)[140]
Included adjuncts to nonsurgical	2	Gerber et al (2016)[133]
		Papageorgiou et al (2015)[142]
Meta-analysis performed		
Meta-analysis of some studies	11	Akram et al (2016)[130,131]
		Chaffee and Weston (2010)[132]
		Li et al (2015)[135]
		Martens et al (2017)[136]
		Moura-Grec et al (2014)[138]
		Nascimento et al (2016)[139,140]
		Nascimento et al (2015)[141]
		Papageorgiou et al (2015)[142]
		Suvan et al (2011)[143]
No meta-analysis	3	Gerber et al (2016)[133]
		Keller et al (2015)[134]
		Martinez-Herrera et al (2017)[137]

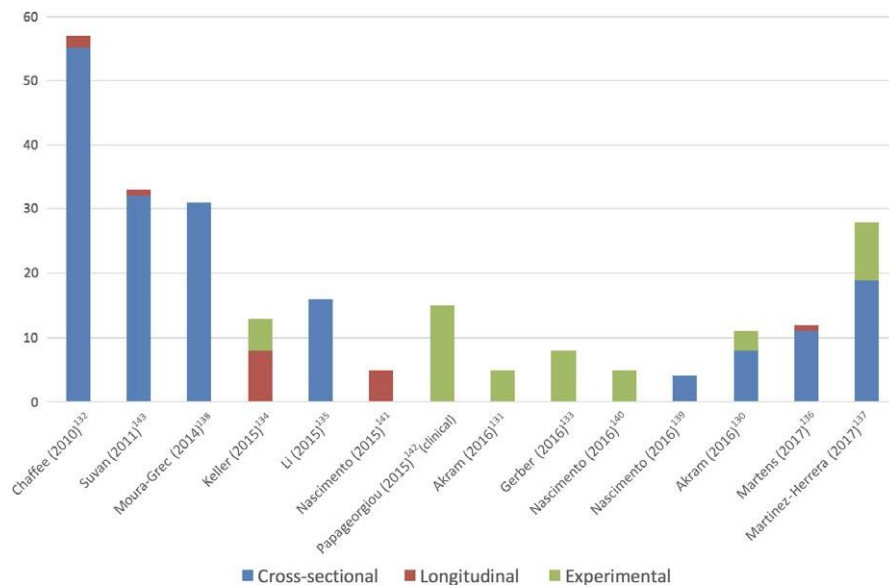**FIGURE 5** Summary of frequency of study designs in systematic reviews

FIGURE 6 Overview of frequency of studies supporting an association between overweight/obesity and periodontal diseases

5 | DISCUSSION

Overall, the findings of this meta-review indicate a positive association between obesity and periodontal diseases in children, adolescents, and adults. Although a large body of evidence for the potentially negative impact of overweight/obesity on periodontal diseases exists, the magnitude and mechanisms of this association still require further clarification.

With all 14 reviews published within a time frame of 7 years, it was anticipated that there would be significant overlap in the articles included; however, this was not the case. As early observational evidence confirming a positive association between prevalence and

incidence, more recent studies have focused on experimental studies or mechanistic aspects, advancing the investigative process of establishing whether or not obesity is a risk factor or risk indicator for periodontal diseases.

Increased odds of having periodontitis if an individual is overweight or obese have recently been confirmed.[144-146] Studies have reported a dose-response relationship for the association between obesity and periodontitis. For example, a cross-sectional investigation in Brazil, reported in 2012, revealed a positive relationship between the prevalence/presence of periodontitis and degree of obesity by comparing periodontal status based on full mouth measurements in women grouped as nonobese, overweight, and World

TABLE 4 Characteristics of included systematic reviews in chronological order of publication

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Chaffee (2010)[132] USA Association between chronic periodontal disease and obesity: A systematic review and meta-analysis	Designs: All study designs other than case series. Human studies. Sample: Adults. Search: MEDLINE, SCOPUS, BIOSIS, LILACS, Cochrane, Brazilian Bibliography of Dentistry databases. Language: English and Spanish. Year: Up to and including July 2010. Aim: To systematically compile evidence of an obesity-periodontal disease relationship from epidemiologic studies, and to derive a quantitative summary of the association between these disease states	Five different definitions/criteria/BMI cut-off points reported to categorize overweight/obesity. Measures reported included BMI, WHR	18 different definitions/criteria reported to categorize as periodontal disease	Number of included studies: 70 studies of 57 study populations, no experimental studies, 2 studies prospective. Meta-analysis: 28 studies. 41 studies showing a positive association. Fixed effect summary association of prevalence of periodontitis and obesity: OR = 1.35 (95% CI: 1.23-1.47). Greater mean clinical attachment loss among individuals with obesity. Higher mean BMI among periodontal patients. Trend of increasing odds of PD prevalence with increasing BMI Many potential confounders among studies	This positive association was consistent and coherent with a biologically plausible role for obesity in the development of periodontal disease. However, with few quality longitudinal studies, there is an inability to distinguish the temporal order of events, thus limiting the evidence that obesity is a risk factor for PD or that periodontitis might increase the risk of weight gain. In clinical practice, a higher prevalence of PD should be expected among obese adults
Suvan (2011)[143] UK Association between overweight/obesity and periodontitis in adults: A systematic review	Designs: All study designs other than case series. Human studies. Sample: Adults. Search: MEDLINE, EMBASE, LILACS, SIGLE. Language: No restrictions. Year: Up to and including December 2009. Aim: To provide a systematic review of the evidence to date investigating the association between overweight/obesity and periodontitis	Eight different definitions/criteria/BMI cut-off points reported to categorize overweight/obesity. Measures reported included BMI, WHR, WC, body fat percentage	16 different definitions/criteria reported to categorize as PD	No. of included studies: 33 (1 longitudinal, 32 observational). Meta-analysis: Overweight/periodontitis: 7 studies. Obese/periodontitis: 12 studies. Overweight/obese/periodontitis: 13 studies. Fixed-effect summary of prevalence of periodontitis and WHO BMI obese: OR = 1.81 (95% CI: 1.42-2.30), WHO BMI overweight/obese: OR = 1.27 (95% CI: 1.06-1.51), and obese/overweight combined OR = 2.13 (95% CI: 1.40-3.26). Heterogeneity among studies noted	These results support an association between BMI representing overweight and obesity and periodontitis although the magnitude is unclear. Additional prospective studies to further quantify or understand the mechanisms of this association are merited. There is insufficient evidence to provide guidelines to clinicians on the clinical management of periodontitis in overweight and obese individuals

(Continues)

TABLE 4 (Continued)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Moura-Grec (2014)[138] Brazil Obesity and periodontitis: systematic review and meta-analysis	Designs: All study designs other than case series. Sample: Humans aged 15 y and older. Search: MEDLINE, EMBASE, LILACS, Cochrane. Language: English, Spanish, and Portuguese. Year: No restriction up to and including December 2010. Aim: To conduct a systematic review of the studies on the association between obesity and periodontitis	Eight different definitions/ criteria/BMIcut-off points reported to categorize overweight/obesity. Measures reported included BMI and, WC	16 different definitions/criteria reported to categorize as PD	No. of included studies: 31 (all cross-sectional). Meta-analysis: 22 studies. Positive association of obesity as a risk factor for periodontitis in 25 studies, 6 did not show a positive association. Compared with normal weight, overweight and obese showed increased odds or periodontal disease OR = 1.30 (95% CI: 1.25-1.35)	Obesity was associated with periodontitis; however, the risk factors that aggravate these diseases should be better clarified to elucidate the direction of this association. Working with paired samples and avoiding confusion factors may contribute to homogeneity between the studies
Keller (2015)[134] Denmark Association between periodontal disease and overweight and obesity: A systematic review	Designs: Longitudinal (cohort) and experimental studies. Sample: Children, adolescents, adults. Search: MEDLINE, Web of Knowledge. Language: Not reported. Year: No restriction up to and including June 2014. Aim: To examine the time-dependent association between obesity and periodontitis in the general population	Overweight/obesity definitions/ cut-off points not reported. Measures reported include BMI and WC	Seven different periodontal outcomes reported; PD and CAL were the most common outcomes. All intervention studies reported on nonsurgical periodontal therapy	No. of included studies: 8 longitudinal. 5 experimental. Meta-analysis: None. 5/8 longitudinal studies: positive association between degree of overweight/obesity and development of periodontitis. 2/5 intervention studies reported better response to therapy in lean patients compared with obese patients. 3/5 intervention studies did not report differences in response to therapy. 1/5 intervention study showed increased response in bariatric surgery patients compared with controls	This systematic review suggests that overweight, obesity, weight gain, and increased WC may be risk factors for development of periodontitis or worsening of periodontal measures

TABLE 4 (Continued)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Li (2015)[135] Hong Kong Anthropometric measurements and periodontal diseases in children and adolescents: a systematic review and meta-analysis	Design: Observational or longitudinal studies. Sample: Children, adolescents. Search: MEDLINE, Web of Knowledge, Cochrane, ProQuest, British Nursing Index, ComDisDome, Gender Watch. Language: English. Year: No restriction up to and including December 2014. Aim: To identify and summarize evidence of the association between anthropometric measurements and periodontal status in children and adolescents	BMI standard categories adjusted for age and WC	Various periodontal outcomes employed including gingival bleeding, loss of attachment, PI, probing pocket depth, CPI, GI, and calculus	Number of included studies: 16. All cross-sectional; 1 on preschool children, 9 on children with mixed dentition, and 6 on adolescents. Meta-analysis: 3 studies. 3 studies: obese compared with nonobese; plaque and obesity OR = 4.75 (95% CI: 2.42-9.34) (P < .001). 3 studies: BOP and obesity OR = 5.41 (95% CI: 2.75-10.63) (P < .001). 2 studies: probing depth >4 mm and obesity no association. 2 studies: subgingival calculus and obesity OR = 3.07 (95% CI: 1.10-8.62) (P < .001)	Obesity is associated with some signs of PD in children and adolescents. Further studies with a comprehensive prospective cohort design and more potential variables are recommended
Nascimento (2015)[141] Brazil Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis	Design: Longitudinal studies. Sample: Adults. Search: MEDLINE, EMBASE, Web of Knowledge, SCOPUS. Language: No language restrictions. Year: No restriction up to and including February 2015. Aim: To conduct a systematic review assessing the effects of weight gain on the incidence of perioBontitis in adults	WHO BMI category cutpoints in all studies. WC reported in 2 studies with differing cut-off points	4 definitions of PD 4 definitions of disease progression	No. of included studies: 5. All prospective. Meta-analysis: 5 studies. Patients in overweight/obese category had higher risk for developing periodontitis than those in BMI nonobese category. Overweight RR = 1.13 (95% CI: 1.06-1.20). Obese RR = 1.33 (95% CI: 1.21-1.47)	A clear positive association between weight gain and new cases of periodontitis was found. However, these results originated from limited evidence. Therefore, more studies with longitudinal prospective design are needed

TABLE 4 (Continued)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Papageorgiou (2015)[142] Germany Effect of overweight/obesity on response to periodontal treatment: Systematic review and a meta-analysis	Design: Randomized and nonrandomized experimental studies. Sample: Adults. Search: Databases not reported. Language: No restrictions. Year: No restriction up to and including July 2013. Aim: To investigate whether the response to periodontal treatment differs among obese, overweight, or nonobese patients	WHO categories of BMI. Overweight/obese grouped together in some studies or analyses and separated in others	Interventions included: • supra-gingival debridement (1/15). • nonsurgical periodontal therapy (8/15). • nonsurgical therapy plus antibiotics (5/15). • nonsurgical therapy plus surgical therapy (1/15)	No. of included studies: 15 4 RCTs and 11 non-RCTs. Meta-analysis: 8 studies (with subgroup analyses in nondiabetic or diabetic population samples) analyzing mean difference from baseline. No statistically significant differences were found in PPD or CAL between overweight/ obese and nonobese groups, between baseline and post therapy. All therapies were grouped together in the meta-analysis. Significant differences in inflammatory and metabolic parameters were based on 1 study in which the level of TNF-a was found to be higher in overweight/obese individuals before treatment and demonstrated greater reduction after treatment compared with nonobese individuals. Mean difference: −1.57 (95% CI: −2.61 to −0.53) pg/mL.	Whereas no difference was found in clinical periodontal parameters, significant differences in inflammatory or metabolic parameters were found between overweight/ obese and nonobese patients, but existing evidence is weak

(Continues)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Akram (2016)[131] Malaysia Efficacy of nonsurgical periodontal therapy in the management of chronic periodontitis among obese and nonobese patients: a systematic review and meta-analysis	Design: Intervention studies. Sample: Adults. Search: MEDLINE, EMBASE, Cochrane, SCOPUS, Google Scholar, Web of Knowledge. Language: Not reported. Year: From 1977 up to and including December 2014. Aim: To evaluate the efficacy of NSPT in the management of CP among obese and nonobese patients	WHO BMI cut-off points were used for defining obesity.	Nonsurgical therapy without adjunctive therapies. Test group: obese. Control group: nonobese. Some studies included smokers and others excluded smokers	Number of included studies: 5. 2/5 studies showed statistically significant differences in clinical parameters, with nonobese subjects demonstrating better periodontal condition following therapy. Meta-analysis: 3. Only 3/5 studies (2 reporting no difference in clinical parameters between obese and nonobese subjects after treatment and one reporting statistically significant difference) reported similar clinical parameters and were combined in meta-analysis; however, heterogeneity was high. No statistically significant differences were reported in clinical parameters (PPD and CAL) between obese and nonobese subjects in the overall mean reported in the meta-analysis. Biomarkers investigated were IL-6, IL-1b, IFN-c, TNF-a, CRP, leptin, and adiponectin: results were variable and inconclusive	It remains unclear whether NSPT has a significantly higher impact on the clinical periodontal outcomes in obese patients than in nonobese patients with chronic periodontitis, given that the number of selected studies was relatively low and the reported findings were inconsistent

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Akram (2016)[130] Malaysia Cytokine profile in chronic periodontitis patients with and without obesity: A systematic review and meta-analysis	Design: Clinical trials, cross-sectional, observational studies. Sample: Adults, adolescents. Search: MEDLINE, EMBASE, Science Direct SCOPUS, Web of Knowledge. Language: Not reported. Year: From 1977 up to and including May 2016. Aim: To systematically review the gingival crevicular fluid cytokine profile in chronic periodontitis patients with and without obesity	Cut-off points used to define obesity in the various included studies were not reported in the review	16 different definitions/criteria were reported to categorize as PD Four studies required >30% of sites to be affected. All samples from GCF	Number of included studies: 11. 8 cross-sectional and 3 intervention studies (non-RCT). Meta-analysis: separate for each of the following cytokines: resistin, adiponectin, TNF-a, resistin, leptin, IL-6, IL-8, IL-1b. Obese subjects versus nonobese subjects with chronic periodontitis: • TNF-a: significant mean difference (P = .004). • IL-6: no mean difference (P = .903). • resistin: significantly higher resistin levels in obese subjects (P = .02). • adiponectin: no mean difference (P = .23). • leptin: no mean difference (P = .87). • IL-8: no mean difference (P = .22). • IL-1b: significant mean difference (P < .001)	The degree of localized periodontal inflammation may have greater influence on the levels of proinflammatory biomarkers in GCF compared with systemic obesity. Whether or not patients with chronic periodontitis and obesity have elevated proinflammatory levels of biomarkers in GCF compared with nonobese individuals remains a matter of debate

(Continues)

TABLE 4   (Continued)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Gerber (2016)[133] Switzerland Influence of obesity on the outcome of nonsurgical periodontal therapy - a systematic review	Design: Intervention studies. Sample: Adults. Search: SCOPUS, MEDLINE, Cochrane, CINAHL, BioSIS, Web of Science. Language: Restricted to English and German. Year: No restriction up to and including January 2016. Aim: To study the hypothesis whether the clinical outcome, in terms of pocket depth reduction, after nonsurgical periodontal therapy in nonobese individuals, is better than in obese individuals	WHO BMI cut-off points used to define obesity	Intervention in all studies was nonsurgical periodontal therapy using hand and/or ultrasonic instruments including oral hygiene instruction	Number of included studies: 8. All interventional. Meta-analysis: None. 3/8 studies failed to show influence of obesity on pocket depth reduction after nonsurgical therapy. 5/8 studies showed a clear negative effect of obesity on the outcome of nonsurgical therapy. Effect noted especially for moderate-to-deep pockets. Significant difference in percentage of pocket reduction to <5 mm following therapy as well as lower mean. PPD reduction in obese individuals compared with nonobese individuals. Obese individuals found to have deeper periodontal pockets at baseline in all studies	The literature on the effect of obesity on the treatment outcome of nonsurgical periodontal therapy remains controversial. The data, however, support the conclusion that obesity is not only a factor associated with poorer periodontal health but might also result in inferior response to nonsurgical treatment of periodontitis
Nascimento (2016)[139] Brazil Is there a relationship between obesity and tooth loss and edentulism? A systematic review and meta-analysis	Design: Observational studies. Sample: Adults. Search: MEDLINE, Web of Knowledge, SCOPUS, SciELO. Language: No restrictions. Year: No restriction up to and including July 2015. Aim: To assess the bidirectional association between tooth loss/edentulism and obesity	Self-reported BMI (1 study). BMI cut-off points combining overweight/obesity (2 studies). BMI WHO Overweight separate from BMI WHO Obese (1 study).	Tooth loss cut-off points included: • 1-5 missing teeth. • 6-31 missing teeth. • edentulous (1/4 studies). • edentulism (1/4 studies). • ≥1 missing teeth (2/4 studies)	Number of included studies: 16 (12 examining impact of edentulism on obesity and 4 considering impact of obesity on edentulism). Meta-analysis: 4 studies considering obesity as exposure. Obese: • OR = 1.49 (95% CI: 1.20-1.86) for any tooth loss. • OR = 1.25 (95% CI: 1.10-1.42) for edentulism	The results indicate a bidirectional association between tooth loss and obesity. Considering that all selected studies were of cross-sectional study design, limiting inferences on temporality, longitudinal perspective studies are required to test the causal relationship between tooth loss/edentulism and obesity or vice versa

TABLE 4 (Continued)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Nascimento (2016)[140] Brazil Does periodontal treatment have an effect on clinical and immunological parameters of periodontal disease in obese subjects? A systematic review and meta-analysis	Design: Intervention studies. Sample: Adults. Search: MEDLINE, EMBASE, SCOPUS, LILACS, Web of Knowledge, SciELO. Language: No restrictions. Year: No restriction up to and including August 2014. Aim: To systematically review literature to answer the questions: • Is periodontal treatment effective to improve clinical and immunological conditions in obese subjects? • Do obese subjects present different clinical and immunological response after periodontal therapy when compared with nonobese subjects?	WHO BMI cut-off points used for defining obese	Nonsurgical therapy without adjunctive therapies. Test group: obese. Control group: nonobese. Some studies included smokers and others excluded smokers	Number of included studies: 5 Same studies included as previous review in table published by Akram et al[131]. Meta-analysis: three Same studies included in one meta-analysis (3/5 studies) as noted in previous review in this table by Akram et al[130,131]. Additional meta-analysis of 2/5 studies did not show evidence of a difference between obese and nonobese individuals in terms of clinical parameters. Obese individuals presented with significantly higher levels of circulating proinflammatory cytokines than nonobese individuals at baseline. No significant differences were found between groups following periodontal therapy	Periodontal treatment seems to be effective for improving healing in obese individuals. No differences were observed in periodontal healing between obese and nonobese subjects; however, only a limited the and fragile base of evidence was available for analysis
Martens (2017)[136] Belgium Association between overweight/obesity and periodontal disease in children and adolescents: a systematic review and meta-analysis	Design: Sample: Children, adolescents. Search: Cochrane, MEDLINE, Web of Science, SCOPUS, SciELO, LILACS, SIGLE. Language: Restricted to English. Year: No restriction up to and including September 2015. Aim: To provide a systematic review and meta-analysis investigating the association between overweight/obesity and periodontal disease in terms of clinical periodontal outcomes in children and adolescents	BMI standard categories adjusted for age, WC, waist/ hip ratio, body fat percentage and skinfold thickness	Various periodontal outcomes employed including gingival bleeding, loss of attachment, PI, probing pocket depth, CPI, GI, calculus	Number of included studies: 12 (11 cross-sectional and 1 longitudinal). Meta-analysis: 7 Association between PD and obesity: OR = 1.46 (95% CI: 1.20-1.77). Positive association reported between overweight/obesity and calculus deposits, gingivitis, gingival bleeding, GI, periodontal index, BOP, PI, and PPD >4 mm	The available evidence suggests a significantly positive association between PD and obesity in children. Pediatric dentists should be aware of periodontal alterations as a potential hazard associated with obesity

TABLE 4 (Continued)

Publication (First author, year, reference number, Country, Article title)	Scope of the review	Overweight/obesity case definitions or related parameters	PD case definition or related parameters	Results	Author conclusions
Martinez-Herrera (2017)[137] Spain Association between obesity and periodontal disease. A systematic review of epidemiological studies and controlled clinical trials	Designs: Observational and experimental studies. Sample: Adults. Search: MEDLINE and EMBASE. Language: Restricted to English. Year: Published from 2000 onward. Aim: To offer a systematic review of the evidence on the association between obesity and PD, and of the possible mechanisms involved in this relationship	All studies included BMI to define obesity and some additionally included WC, WHR or percentage of body fat	Definition of periodontitis was based on PPD, CAL, PI, BOP, ABL, self-reporting, and GI, with thresholds not reported	Number of included studies: 29 (19 observational and 9 experimental). Meta-analysis: None. Results of observational studies demonstrate a higher prevalence of periodontal disease in obese individuals than in nonobese individuals with a stronger association as obesity level increases. Some studies support the association between obesity and the development of periodontitis or weight gain and the development of periodontitis. Studies reporting on response to therapy were inconsistent so the effect of obesity on response to periodontal treatment remains unclear	The association between obesity and periodontitis was consistent with a compelling pattern of increased risk of periodontitis in overweight or obese individuals. Although the underlying pathophysiological mechanism remains unclear, it has been pointed out that the development of insulin resistance as a consequence of a chronic inflammatory state and oxidative stress could be implicated in the association between obesity and periodontitis

95% CI, 95% confidence interval; ABL, alveolar bone loss; BMI, body mass index; BOP, bleeding on probing; CAL, clinical attachment level; CP, chronic periodontitis; CPI, Community Periodontal Index; CRP, C-reactive protein; GCF, gingival crevicular fluid; GI, gingival index; IFN-c, interferon-gamma; IL, interleukin; NSPT, nonsurgical periodontal therapy; OR, odds ratio; PI, plaque index; PD, periodontal disease; PPD, periodontal probing depth; RCTs, randomized controlled trials; RR, relative risk; TNF-a, tumor necrosis factor alpha; WC, waist circumference; WHO, World Health organization; WHR, waist/hip ratio.

TABLE 5 Quality assessment of included publications according to A MeaSurement Tool to Assess systematic Reviews (AMSTAR)

Author, year (reference number)	Was an a priori design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (ie, grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Was scientific quality of the included studies assessed and documented?	Was scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Were potential conflicts of interest included?	AMSTAR risk of bias score
Chaffee and Weston (2010)[132]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	8/10
Suvan et al (2011)[143]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	9/10
Moura-Grec et al (2014)[138]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Unclear	Yes	7/10
Keller et al (2015)[134]	Yes	Yes	Unclear	No	Yes	Yes	Yes	Not applicable	Unclear	Yes	7/10
Li et al (2015)[135]	Yes	Yes	Yes	No	Yes	Yes	Yes	Partially	Unclear	No	6/10
Nascimento et al (2015)[141]	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Unclear	Yes	8/10
Papageorgiou et al (2015)[142]	Yes	Partially	Databases not reported	Databases not reported	Yes	Yes	Yes	Yes	Unclear	Yes	6/10
Akram et al (2016)[130]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	8/10
Akram et al (2016)[131]	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Unclear	Yes	7/10
Gerber et al (2016)[133]	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Unclear	Yes	8/10
Nascimento et al (2016)[139]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	8/10
Nascimento et al (2016)[140]	Yes	Yes	Yes	No	Yes	Yes	Yes	Partially	Unclear	Yes	7/10
Martens et al (2017)[136]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	9/10
Martinez-Herrera et al (2017)[137]	Yes	Not reported	Yes	No	Yes	No	No	Not applicable	Unclear	Yes	5/10

Health Organization obesity levels I, II, and III. The reported odds ratios were 1.20, 1.46, 1.78, and 2.31, respectively, for each body mass index group, inferring a dose-response association.[147] A statistically significant association between the number of teeth with deepened pockets and body mass index, body fat percentage, and waist circumference was demonstrated in a Finnish population sample.[148] While such results warrant further confirmation, more recent investigations have highlighted possible contributing factors. A cross-sectional study conducted in Brazil reported obese cases to have a higher risk of unfavorable periodontal status, with a relative risk of 1.45 for attachment loss. Furthermore, the study compared abdominal obesity with general obesity and reported no evidence of the effect of the latter on bleeding on probing, whilst the former was linked to periodontal attachment loss and bleeding on probing.[146]

Studies of disease onset or progression are infrequent but some have reported on the association between obesity and periodontitis progression, with 5 of 8 supporting a temporal sequence between them. In a 5-year follow-up study of 3590 Japanese individuals, a linear relationship between periodontitis progression and body mass index was observed.[149] In 2 studies based on the examination of 1038 US veterans as part of a 40-year health survey, body mass index, waist circumference, and waist circumference-to-height ratio were all significant predictors of periodontitis progression in men, with those who gained weight most rapidly presenting with higher levels of periodontal attachment loss.[150,151] A recent subgroup analysis of 292 men from the same cohort suggested that the association of central adiposity and progression of periodontitis is attenuated by genetic variants of proinflammatory interleukin-1.[152] A retrospective analysis of 582 individuals who were part of the Porto Alegre Epidemiological study demonstrated that obese individuals had a higher risk of periodontal attachment loss than nonobese individuals (relative risk = 1.36 [95% CI: 1.04-1.78]). A stratified analysis demonstrated that the association was present for female subjects (relative risk = 1.64 [95% confidence interval: 1.11-2.43]) but not for male subjects (relative risk = 1.13 [95% confidence interval: 0.75-1.69]).[153]

Reviews of experimental studies produced varying results and conclusions on the association of overweight/obesity with inferior response to periodontal therapy. This may have occurred for reasons associated with the heterogeneity of the design of the studies included. For example, in one review, all experimental studies included failed to show a positive association.[142] This review was unique because it included studies on patients with and without type 2 diabetes as well as interventions with adjunctive use of systemic antibiotics, each of which may have masked the effects of other factors, such as obesity. Many of the studies investigating the clinical response to periodontal therapy included in the reviews were conducted on a small sample of patients and did not report calculation of a sample size; therefore, uncertainty remains regarding the validity of any difference demonstrated.[154-156] Meta-analysis of small studies may help overcome this issue; however, it was not possible to do so here because of the high levels of heterogeneity

of the included studies in terms of participant inclusion criteria, interventions administered, and reported outcomes. For example, 1 study based analysis of the effect of obesity on response to treatment between study groups on sites with probing depths ≥4 mm following treatment no statistically significant difference was shown.[157] This study was 1 of 3, included in the review by Gerber et al,[133] which did not demonstrate a difference in periodontal clinical parameters in obese versus nonobese subjects following treatment. Five of 8 studies in this review did report poorer clinical responses to periodontal treatment in obese compared with nonobese subjects, with the comment that the effect was specifically observed in moderate-to-deep pockets.[133] Therefore, the difference reported in studies of periodontal therapy may be attributed, in part, to baseline severity of disease and thresholds used for analysis.

The included reviews that reported on surrogate measures of association between periodontitis and obesity (ie, soluble markers) demonstrated variability in results; this was partly because of the type of sample selected (gingival crevicular fluid, serum, or plasma) and the specific biomarkers analyzed. One of the reviews focused solely on assessing the cytokine profiles in gingival crevicular fluid from chronic periodontitis patients with and without obesity; 8 reported a similar cytokine profile (of resistin, adiponecin, leptin, interleukin-6, interleukin-8, interleukin-10, and interleukin-1beta) in obese and nonobese subjects; whereas 5 reported greater differences in some cytokines (resistin, interleukin-8, interleukin-1beta, tumor necrosis factor alpha, progranulin, monocyte chemotactic protein-4, and lipocalin).[130] However, some studies did not standardize the methodology of gingival crevicular fluid collection and/or did not report exclusion of participants based on the presence of other systemic diseases, such as diabetes. Changes in clinical parameters following periodontal therapy were not consistently reflective of changes in local or circulating biomarker analyses.[130,131,137,140,142]

Additional reports of biomarker analyses have been published in 2016-2017, some of which are discussed within the context of our current understanding of possible mechanisms of the association between obesity and periodontal diseases. Two recent publications investigated the impact of obesity on periimplant inflammation by comparing clinical parameters and either periimplant sulcular fluid or whole saliva.[158,159] Elangovan et al[159] reported a statistically significant correlation between interleukin-1beta in peri-implant sulcular fluid and waist circumference in 73 periodontal maintenance patients with implants. In a study of 72 men, mean periimplant probing depth and bleeding on probing were statistically significantly higher in obese than in nonobese individuals. Salivary levels of interleukin-1beta and interleukin-6 were also higher in obese individuals.

5.1 | Possible mechanisms

Published reports of the possible mechanisms or pathways connecting obesity and periodontal diseases continue to increase our understanding of the complexity of the association. An exaggerated host immune response was initially reported in an experimental model of

periodontal bone loss.[116] Clinical evidence confirmed that obese individuals have an increased local inflammatory response[160] as well as an altered periodontal microflora.[161] As the host response to local bacterial challenge is a key factor in the pathogenesis of periodontitis, differences in the oral microbiome, together with an altered host response in obesity, have been investigated. Reports of the oral/periodontal microbiome composition in overweight and obese individuals remain few in number. A recent observational study reported obesity to be associated with increased proportions of periodontal pathogens, particularly in patients with obesity and chronic periodontitis, but also in obese individuals without periodontitis.[162] An investigation of obese individuals after bariatric surgery and an obese control group with or without periodontitis compared the oral and gastric presence of periodontal pathogens and Helicobacter pylori. Higher frequency of H. pylori was reported in both oral and stomach environments in patients who had undergone bariatric surgery compared with the obese control group (no surgery).[147]

An alternative mechanism behind this association could be the altered insulin sensitivity state found in obese individuals.[163] Research suggests that reduced insulin sensitivity coupled with increased production and accumulation of advanced glycation endproducts at the gingival level in people with diabetes can result in greater periodontal tissue destruction.[39,164] Researchers in Spain evaluated 110 obese and 102 lean individuals to determine the role of insulin resistance in the association between obesity and periodontitis. Individuals were divided into nonobese and obese groups, with and without insulin resistance, and were then assessed for inflammatory markers and periodontal status. In agreement with reports presented in the systematic reviews, the results showed that periodontitis was more prevalent and greater in extent and severity in obese subjects than in lean individuals, but was most extensive in obese subjects with insulin resistance.[145]

Chronic periodontitis has been suggested as a distant source of inflammatory by-products affecting insulin sensitivity.[164] Tumor necrosis factor alpha is one of the cytokines secreted by visceral adipose tissue in particular, and is implicated in mediation of endotoxin-induced injury in periodontal tissue.[165] The concentrations of tumor necrosis factor alpha have been reported to be higher in patients with periodontitis compared with periodontally healthy patients, and have been shown to be reduced following periodontal therapy.[161] In the previously mentioned study investigating the role of insulin resistance, the levels of tumor necrosis factor alpha and high sensitivity C-reactive protein were higher in all obese subjects than in nonobese subjects.[145] Higher levels of tumor necrosis factor alpha in gingival crevicular fluid has been shown to be associated with a body mass index of ≥ 40.[75] An association of tumor necrosis factor alpha in gingival crevicular fluid with body mass index has also been demonstrated in obese subjects without periodontitis. It is suggested that tumor necrosis factor alpha found in gingival crevicular fluid of obese subjects may be secreted from the adipose tissue.[164]

Production of reactive oxygen species resulting in oxidative stress has been investigated as a pathway that may be linked to insulin sensitivity and contributing to a proinflammatory state in obese individuals. An early study showed secretion of reactive oxygen species to be upregulated in adipose tissue and the liver of mice on a high fat diet.[166] Oxidative stress has also been implicated in severe periodontitis with the suggestion of obesity playing a contributing role.[167,168] This notion is supported by a study that compared oxidative stress in nonobese and obese subjects who were periodontally healthy or had gingivitis or periodontitis. They found oxidative stress to be higher in the obese plus chronic periodontitis group compared with the nonobese plus chronic periodontitis group; higher in the obese plus gingivitis group compared with the nonobese plus gingivitis group; and higher in the periodontally healthy group compared with the periodontally healthy nonobese group.[169] In a similar study design (4 groups), Suresh et al[170] also reported more oxidative stress in obese individuals with periodontitis compared with periodontally healthy individuals with obesity.

Leptin, also secreted from adipose tissue, plays a role in immune system function and it is suggested that it plays a role in the pathogenesis of chronic inflammation, with the elevated levels of leptin in obesity believed to contribute to the low-grade inflammation.[171] Reports of leptin levels in gingival crevicular fluid or saliva have been inconsistent.[130] Evidence of the association of elevated circulating levels of leptin in obese individuals with periodontitis continue to emerge. Thanakun et al[172] reported higher levels of tumor necrosis factor alpha, interleukin-6, leptin, and C-reactive protein in overweight and obese individuals with periodontitis compared with their nonobese counterparts. Adiponectin (anti-inflammatory) was found to be present at lower levels in overweight/obese individuals with periodontitis. A recent cross-sectional analysis of the levels of resistin, adiponectin, leptin, tumor necrosis factor alpha, and interleukin-6 in the gingival crevicular fluid of nonobese and obese subjects, with and without periodontitis, concluded that obesity stimulated upregulation of local tumor necrosis factor alpha and serum interleukin-6, the levels of which were highest in the obese group with periodontitis. The levels of adiponectin were decreased, whereas the levels of leptin in gingival crevicular fluid did not differ between groups.[173] Kanoriya et al[174] compared gingival crevicular fluid and serum levels of leptin in 70 individuals divided into obese and nonobese groups with or without periodontitis, and found that elevated serum levels of leptin correlated to level of obesity and periodontal health, with the obese periodontitis group demonstrating the highest levels (nonobese periodontally healthy subjects had the lowest levels of leptin), while gingival crevicular fluid levels of leptin were inconsistent among the groups.

Dyslipidemia is a clinical condition proposed to be associated with periodontitis in addition to obesity, diabetes or vascular disorders. It is suggested that dyslipidemia may exist as a link between obesity and periodontitis. Cury et al[175] recently investigated serum levels of lipids in nonobese and obese patients with or without periodontitis. Their results showed that periodontitis and obesity, jointly or individually, were associated with poorer lipid profiles, with obese individuals with periodontitis demonstrating the poorest profiles. Zuza et al[176] also reported poorer lipid profiles in obese compared

with nonobese individuals, with lipid profiles of all subjects with periodontitis being altered following nonsurgical therapy in the obese group.

Evidence also exists of a link between different gene expression profiles and obesity/periodontitis. After inducing experimental periodontitis in obese Zucker rats, Endo and coworkers[177] concluded that systemic low-grade inflammation after inducing experimental periodontitis was associated with gene expression of transcribing C-reactive protein, interleukin-6, and tumor necrosis factor alpha in the liver, and C-reactive protein and interleukin-6 in white adipose tissue, accounting for the higher susceptibility of obese Zucker rats. O'Neill et al[178] highlighted the important role of toll-like receptors (specifically toll-like receptor 4) as part of the innate immune response regulating macrophages. It was later demonstrated that one means by which toll-like receptor 4 affects macrophages is through the increase or decrease in microRNA-107.[179] A recent report highlights a modulating action of specific microRNAs (microRNA-200b and microRNA-200c) on cell lines including macrophages, resulting in downregulation of the nuclear factor kappa-light-chain-enhancer of activated B-cells pathway (which is toll-like receptor 4 dependent).[180] It is possible that microRNAs modified in obesity may affect the inflammatory gene targets that predispose to periodontitis.[181] The increase in adipokines released from adipocytes triggers macrophage infiltration and the release of cytokines such as interleukin-1beta, interleukin-6, and tumor necrosis factor alpha, leading to insulin resistance and the induction of more inflammation.[182]

In efforts to understand mechanisms of association between obesity and comorbidities, such as periodontal diseases, substances associated with appetite and consumption of nutrients have been investigated. Ghrelin, one of the hormones secreted by stomach cells, plays a role in energy balance through stimulation of appetite. It stimulates growth hormones, but also plays a part in insulin release. A cross-sectional comparison of overweight/obese subjects with nonobese individuals, with and without periodontitis, demonstrated that ghrelin levels in gingival crevicular fluid were significantly lower in individuals with chronic periodontitis and overweight/obesity (median = 118 pg per site) compared with lean individuals with chronic periodontitis (median = 140 pg per site), or periodontally healthy individuals with overweight/obesity (median = 145 pg per site).[183]

Understanding the complex interplay of all mediators and factors determining a dysregulated or altered homeostasis in inflammatory and immune responses in patients with obesity and periodontitis remains the pursuit of many. Figure 7 is a proposed model outlining current understanding of the signaling pathways that may underpin the relationship between obesity and periodontitis.

The host systemic inflammatory response (mounted by the liver) lies at the center of the various pathways implicated in the association between overweight/obesity and periodontitis. Adipose tissue (fat cells) secrete proinflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6, that are key inducers of the acute phase hepatic response, resulting in an increased level of C-reactive protein. Adipocytokine secretions may contribute to this hepatic response, including an increase in reactive oxygen species and free
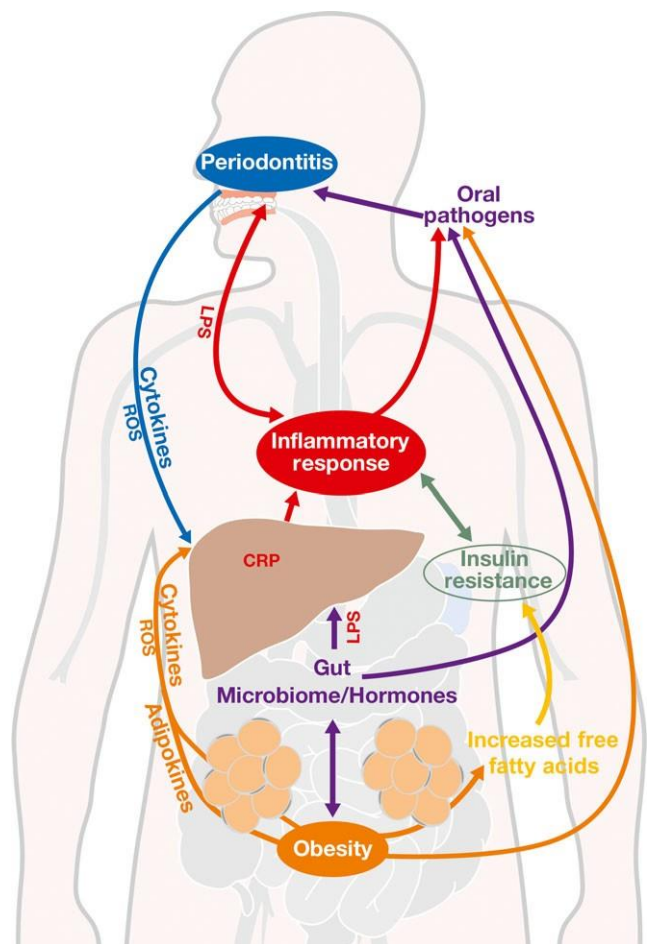

FIGURE 7 Signaling pathway depicting possible links among obesity, inflammation and periodontitis. CRP, C-reactive protein; LPS, lipopolysaccharide; ROS, reactive oxygen species

fatty acid production (ultimately contributing to insulin resistance), as well as altering the gut microbiome or hormone production. Lastly, altered gut permeability with leaking lipopolysaccharide molecules could contribute to this general state of chronic inflammation identified in obese individuals. The resultant increased inflammatory response may, in turn, contribute to alteration of the oral microbiome and/or the local gingival responses to bacteria. Furthermore, it has been proposed that obesity is associated with altered microflora via more direct pathways (possibly associated with dietary choices). Once periodontitis is established, the local inflammatory and infectious burden contribute to stimulate the host hepatic response further, via increased systemic dissemination of bacterial end products (lipopolysaccharides) and proinflammatory cytokines (such as tumor necrosis factor alpha and interleukin-6), as well as increased production of reactive oxygen species.

6 | IMPLICATIONS FOR HEALTH PROFESSIONALS

This meta-review highlights the importance of risk assessment as an essential part of patient care. This concept is based on the

current understanding that periodontitis is a multifactorial chronic disease with susceptibility varying from one individual to another. Specific targeting of therapies according to estimated risk of each patient has been proposed as the key to periodontal disease management.[50]

Increasing evidence of obesity as a risk indicator for periodontitis is merely a beginning and does not yet facilitate our understanding of the possible impact for patient care. Questions arise regarding the ways possible to assess or quantify the risk at the level of an individual patient or a tooth. As there are minimal data on the potential benefit of weight loss in reducing the injurious and additive effect of obesity on periodontal disease, we are unable to choose and recommend treatment regimens that might work best to compensate for the effect of obesity. With insufficient evidence to guide specific treatment strategies for obese individuals, professionals should not limit clinical judgements to body mass index thresholds or other measures of overweight/obesity, but rather should adhere to known principles of evidence-based and personalized healthcare, making clinical decisions that incorporate individual patient characteristics. This demands an increasingly interactive approach to patient care that is focused on healthy lifestyle strategies to address modifiable risk factors supplemented by personalized choices of professionally rendered therapies.

In the context of overweight and obesity, the first step might be for every dental professional to incorporate recordings of height and weight (with subsequent calculation of body mass index) into daily practice as a part of risk assessment. Additionally, assessing fat distribution by measuring waist circumference could add to risk stratification. Both measures could increase awareness of overweight and obesity with patients. Similarly to the issue of self-awareness and reporting of smoking, people tend to underestimate their weight but tend to overestimate their height, resulting in a misconception of their body mass index.[184,185] As a consequence of not knowing their body mass index category, many people may not associate the health risks that they hear are related to a high body mass index as something that is relevant for them.

Likewise, it is proposed that practitioners caring for patients with obesity should be aware of the possible increased risk of periodontitis in their obese patients, and of its potential to add to the already obesity-related elevation in cardiovascular risk. While obesity management may not yet be proven to reduce this, periodontal treatment certainly has been, and should therefore be a mandatory part of comprehensive care, with possibly even referral for periodontal assessment, as has already been proposed for professionals treating patients with diabetes.[50]

In August 2013, The Lancet published a comment statement entitled "A milestone in the response to noncommunicable diseases"; priorities published in April 2011 were adopted as a Global Action Plan for Prevention and Control of Non-communicable Disease 2013-2020 by 194 World Health Organization member states.[186] The action plan proposes a multifaceted collaborative approach to involve health professionals, industry, governments, and the public in reducing the common modifiable risk factors for noncommunicable

diseases.[187] It is suggested that dental professionals could play a role in this collaborative approach.

7 | IMPLICATIONS FOR RESEARCH

The results of this meta-review suggest that further studies are required to replicate the current findings in specific population samples in order to explore differences according to age, gender, ethnicity, or other possible confounding factors. There are several population-based prevalence studies that show the association at a population level, and further research in this area should be based on published standardized definitions of disease onset, presence, and progression, to understand the magnitude of effect of overweight/obesity. These studies should include more precise phenotyping of body composition and fat distribution, to facilitate understanding of the correlation of each method of assessment with periodontal outcomes.

Sufficient evidence is available to allow the design of studies of possible interventions or treatment regimens as part of the management of oral health in overweight and obese individuals. These studies should include longer follow-up to facilitate understanding of the elements of secondary prevention (periodontal maintenance therapy), and should test interventions and strategies that would be feasible for practitioners in routine care.

Further studies investigating systemic biomarkers are indicated to advance knowledge of possible mechanisms linking overweight/obesity and periodontitis. These studies could lead to a better understanding of mechanisms responsible for the association between periodontitis and obesity, and open new avenues for the identification of therapeutic targets in order to maximize treatment responses and disease management.

8 | CONCLUSIONS

In conclusion, the results presented in this meta-review support the notion of obesity as a factor contributing to periodontal complications. Specifically, the included systematic reviews provide evidence of an association between overweight/obesity and the prevalence, extent, and severity of periodontal diseases, and treatment response in all age groups. In the context of personalized and predictive medical models that suggest the importance of risk assessment, these findings suggest that dental professionals should consider assessment of body mass index as part of daily practice as a means of assessing patients, with the intent to individualize preventive and treatment strategies. Furthermore, assessment and discussion of risk associated with overweight/obesity serves to increase patient awareness of obesity as a chronic disease and serious health condition. Although evidence is lacking to provide specific guidelines to clinicians on the management of periodontal diseases in overweight and obese individuals, awareness of the potential for increased risk of periodontal complications is important. Obesity experts should be aware of the increased risk for

periodontal complications in overweight/obese patients, and should be prepared to refer patients to dental professionals for further care. Additional prospective studies, to further quantify the magnitude of this association and understand the exact mechanisms, together with studies of periodontal interventions in obese individuals, are merited.

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