Periodontitis and Systemic Diseases

Clinical Evidence and Biological Plausibility

Josefine Hirschfeld
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Preface

The training of dental and medical students has diverged in recent decades along distinct pathways. Medical courses devote a trivial amount of time to the study of the oral cavity, presuming it to be the sole responsibility of oral health care professionals. Similarly, dental programmes cover the entirety of human diseases and the underpinning biological and pharmacological sciences as relatively minor components of a long programme of study, presuming it to be the unique responsibility of medical professionals. Hence, the mouth has become figuratively separated from the rest of the body. However, the mouth represents one of the most complex organs of the human holobiont, as well as one of the most vulnerable points of entry for microbial pathogens into the internal systems and structures of the body. Teeth naturally breach the ectodermal barrier of the oral mucosa (gingiva), and form a non-shedding surface that is colonised by the second most complex human microbiome. Nature has therefore created a unique anatomical and physiological barrier to isolate mesodermal and ectodermal tissues, which is composed of the junctional epithelium, immunological surveillance processes, and the gingival crevicular fluid. The vulnerability of this complex results in micro-ulcers that form following dental plaque biofilm accumulation, and a portal of entry for the microbiome into the internalised body systems develops. The downstream consequences are both significant and under-appreciated. It is therefore unsurprising that in recent decades, periodontitis has become recognised as a significant and independent risk factor for premature mortality, and multiple chronic non-communicable diseases associated with ageing. This book attempts to provide a contemporary evidence base for periodontal-systemic disease relationships, from epidemiology, to the biological plausibility of associations, to considerations of causal pathways and therapeutic challenges. It aims to put the mouth back inside the body for both dental and medical professionals, and in doing so, makes a compelling case for a reunion of these two professions. From such a reunion, collaborative care pathways can be developed that embrace both personalised and precision medicine, and place the individual at the centre of holistic care. It is time to break down the artificial barriers that have emerged from 20th century educational theory and practice.

Iain L.C. Chapple & Josefine Hirschfeld

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Dr Hirschfeld would like to dedicate this book to her loving, supportive and encouraging family. She also wishes to acknowledge the role of her past and current teachers and mentors in Würzburg, Boston, Bonn and Birmingham, in developing and inspiring her academically and scientifically.

Prof Chapple wishes to dedicate this text to his late mother Beryl Chapple and his father Arthur Chapple for their devoted care and guidance. He wishes to thank his wife Liz and daughters Jess and Tasha for their unconditional support, love and patience.

Both editors are extremely grateful to the chapter authors for their dedication, expertise and friendship in creating this book and for their commitment to our discipline, our patients and the public at large. They also wish to dedicate this book to two giants of this area of study, Robert Genco (1938–2019) and Stephen Offenbacher (1950–2018) – thank you Bob and Steve for your science, mentorship and friendship – this is your legacy.

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Contents

Introduction

Josefine Hirschfeld and Iain L. C. Chapple

Periodontitis is a highly prevalent chronic inflammatory disease that impacts 45% to 50% of adults worldwide, with severe disease affecting 7.4%[1] to 11.2%[2]. The global incidence of severe periodontitis in 2015 was 6 million, accounting for 3.5 million disability associated life years (DALYs, a measure of disease burden, expressed as the number of years lost due to morbidity), compared with 1.7 million DALYs for untreated caries in adult teeth; more than any other oral disease[1]. Moreover, the indirect cost to the global economy in 2015 of severe periodontitis was estimated at US $54 billion in productivity losses[3] and the human cost is also significant in terms of reduced nutrition, social confidence and oral health-related quality of life. Periodontitis prevalence increases with age, with a steep incline between the third and fourth decades of life. Due to the growing world population, associated with an increasing life expectancy and a decrease in the prevalence of caries-related tooth loss in many countries[1], the burden of periodontitis is expected to increase.

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterised by progressive destruction of the tooth-supporting tissues. Its primary features are presence of periodontal pocketing and radiographically assessed alveolar bone loss, and can also include signs of gingival inflammation such as redness, swelling and bleeding of the gingiva. Periodontitis is a major public health problem due to its high prevalence, and because it often leads to tooth loss when left untreated. This can result in reduced chewing function and aesthetics, and can further exacerbate oral pathology by leading to pathological tooth migration and occlusal trauma as well as periodontal–endodontic lesions. Therefore, periodontitis directly impairs quality of life[4].

Many aspects of the pathophysiology of this inflammatory condition have been characterised. It is recognised that periodontitis has multiple component causes, which when combined in each individual can exceed a threshold for disease initiation[5]. Examples include:

- an aberrant host immune-inflammatory response to the dental plaque biofilm
- dysbiosis within the biofilm, which contains higher proportions of Gram-negative, anaerobic and facultative bacteria and is microbially less diverse than a healthy biofilm
- genetic and epigenetic factors affecting immune responses and tissue homeostasis
- older age, leading to immune senescence and consequent hyper-inflammatory responses, termed ‘inflammaging’
- modifiable lifestyle factors such as suboptimal oral hygiene, smoking, high stress levels and diets high in refined sugars and low in antioxidant micronutrients
- certain systemic conditions, which affect the immune system and which are discussed in this book.

Environmental factors may also contribute to the onset and progression of periodontitis, but these are currently less well understood. The dysregulated immune reactions ultimately lead to host-mediated damage and breakdown of the periodontal tissues including the alveolar bone. Clinical phenotypes may vary, with some patients presenting with severe periodontal breakdown at a relative young age.

Importantly, there is now abundant evidence that untreated periodontitis promotes the translocation of dental plaque-derived microorganisms, their antigens and certain metabolic components into the circulation, where they may elicit systemic inflammation via an acute-phase response and oxidative stress. This systemic dissemination of antigens and inflammatory mediators has been proposed to form the basis of the association between periodontitis and mortality and also with several systemic non-communicable diseases (NCDs), in conjunction with other mechanisms specific to those diseases[6]. Numerous clinical and experimental studies have been undertaken in recent decades to better define the association between periodontitis and several systemic NCDs. However, these

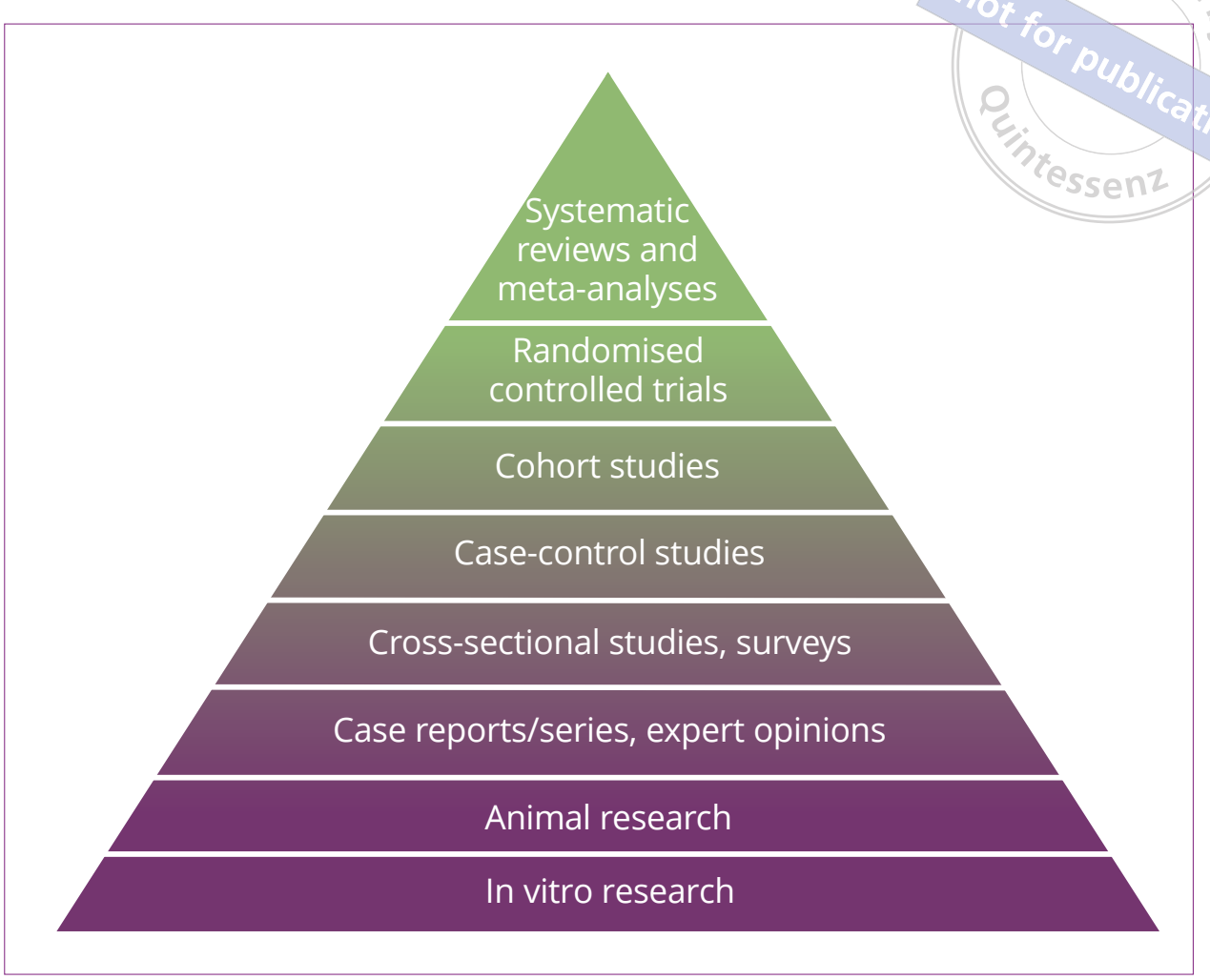

Fig 0-1 Evidence-based medicine pyramid.

studies differ markedly in design and quality. In some clinical studies, inconsistent use of case definitions of disease, insufficient control of biases and small sample sizes render results difficult to interpret. Moreover, changes in disease classification systems make comparisons between studies published over several decades challenging. However, the new classification system of periodontal and peri-implant diseases and conditions[7], as well as recently updated case definitions for periodontitis[8] will help to create greater consistency in clinical periodontal research. Furthermore, the advent of international standards and guidelines for conducting and reporting studies has introduced more consistency and clarity and has improved the quality of those studies adhering to them. Some examples are PRISMA for meta-analyses, CONSORT or STROBE for clinical studies, ARRIVE for animal studies[9] and MIQE or MIAPE for experimental ex vivo studies[10].

Prior to reading this book, it is important to consider certain principles. First is the principle of evidence-based medicine, which acknowledges that a hierarchy of evidence exists[11]. This helps practising clinicians and researchers appraise literature and apply evidence to their work, based on the relative strengths and weaknesses of individual study designs. This hierarchy can be depicted as a pyramid, often referred as to the 'evidence-based medicine pyramid' (Fig 0-1). The pyramid is divided into levels, where each represents a different type of study

design and corresponds to increasing rigour, quality and reliability of the results, and also to higher costs of conducting the relevant studies.

The first three levels of the pyramid provide the foundation of knowledge. This background information is important and helpful, but can be heavily influenced by beliefs, opinions and even political views. The top of the pyramid suggests a lower risk of statistical error and bias from confounding variables. Cross-sectional and case-control studies represent the first stage of testing an observation. These studies are conducted in the early stages of research to help identify variables that might be associated with a condition. One of the weaknesses of these designs is that there are often small sample sizes and they are usually non-randomised. The next evidence level is that of prospective cohort studies, which follow people, who are exposed to the suspected risk factor for a disease, over a period of time. Here, causality can be assessed, but cohort studies require large sample sizes and long follow-up times, making them more difficult to apply to diseases with a long latency, such as periodontitis, or for rare conditions. Large double-blind randomised controlled trials are the most reliable study designs and provide the strongest level of evidence for cause and effect relationships. However, these studies are expensive and can be ethically problematic.

Systematic reviews and meta-analyses are located at the top of the pyramid and compare the results of studies side by side. Multiple studies are reviewed using a systematic approach and, where studies are not too dissimilar in design (show low heterogeneity), a statistical summary (meta-analysis) is undertaken that summarises the effect of an intervention, the influence of a risk factor or other outcomes across multiple studies. They are considered as providing the strongest and highest quality of evidence. However, results strongly depend upon the quality and comparability of the included studies. Cochrane publishes systematic reviews with the highest level of rigour and techniques to identify the risks of bias in systematic reviews[12].

Next is the distinction between an association and a causal relationship between two or more diseases. An association is when two conditions are related such that they are commonly observed together. A causal relationship between two conditions implies that a change in one is caused by a change in the other. Causal relationships are stronger than associations, but also more difficult to prove. An example for distinguishing between these two is the following fictional research question: if researchers included coffee drinkers and non-coffee drinkers in their cross-sectional study, they may find that a greater proportion of coffee drinkers have periodontitis, compared with non-coffee drinkers. This is an association, which does not imply that coffee drinking causes periodontitis, but merely that coffee drinking and periodontitis are commonly observed together.

What would be more interesting, however, is whether coffee drinking is a component cause or part of the causal pathway of periodontitis. The causal argument can be strengthened in cross-sectional studies by accounting for things that might confound the association. In our example, it may be that people who drink coffee have higher stress levels or are more likely to smoke and therefore more likely to have periodontitis. Hence, smoking and/or stress is confounding the association observed. There are several ways of eliminating or minimising the effect of confounders. If they are known and measurable, they can be eliminated in the design of the study, for instance by excluding smokers and observing whether non-smoking coffee drinkers have a higher prevalence of periodontitis than non-smoking non-coffee drinkers.

Another method of minimising the effects of confounding is using a stratified analysis. If our fictional research was conducted in smokers as well as non-smokers, the results could be analysed separately in both groups. If the association was then found to be of a similar magnitude in both, smoking would be unlikely to be a confounder of the relationship. A further method of accounting for the potential presence of confounders is in the statistical analyses by employing regression modelling tech-

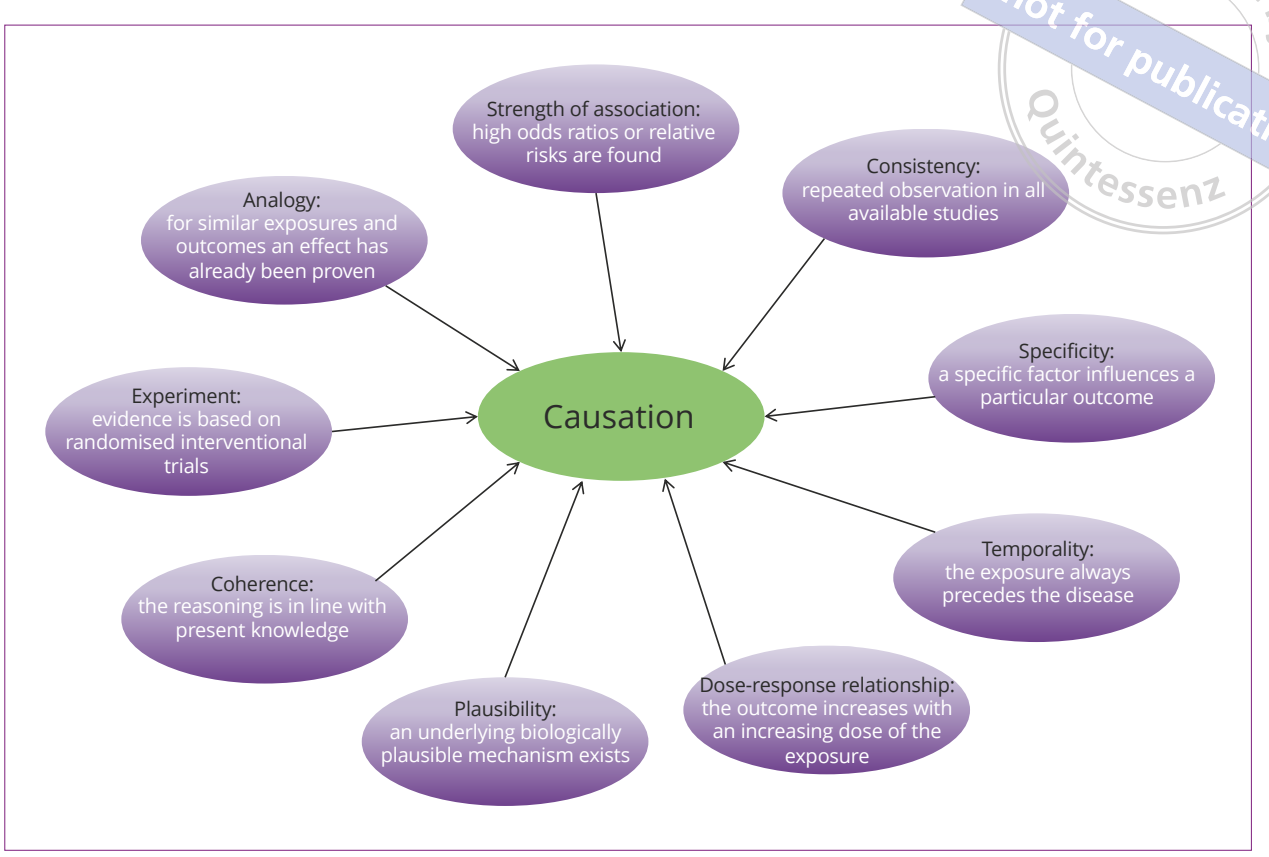

Fig 0-2 Bradford-Hill criteria: the nine aspects of association providing epidemiological evidence of a causal relationship between a presumed cause and an observed effect.

niques, sometimes referred to as 'adjusted analyses'. The basic premise of all these techniques, however, is that the confounder needs to be known, and needs to be easily, accurately and reproducibly measurable. This can sometimes be difficult, for example in the case of determining the socio-economic status of study participants. The ideal way of eliminating the problem of confounding is the process of randomisation. If the randomisation is robust, the arms should be equivalent in both known and unknown confounders, hence comparisons between the arms are devoid of these problems. Thus, randomised controlled trials and meta-analyses thereof form the pinnacle of the evidence-based medicine pyramid.

The criteria set out by Austin Bradford Hill, in 1965, represent a useful tool in guiding from association to causation (Fig 0-2). In this classic essay, Bradford Hill set out some aspects of association, which should be considered "before deciding that the most likely interpretation of it is causation"[13]. These included:

- **The strength of the association**. If the magnitude of the association is large, for example as measured by a high odds ratio or relative risk, it is more likely that the association will not be attenuated by some unmeasured or imperfectly measured variable. This makes the association more likely to be causal.
- **Consistency**. If an association has only been observed by one group at one time, it is likely to be artefactual. Reproducibility of the association from different populations at different times and or locations lends credence to the association.
- **Specificity**. This property relates to the association seen between two, very specific, condi-

tions. The more specific an association between a factor and an effect, the greater the probability that it is causal. If this criterion is not met, however, it does not imply a lack of causation.

- **Temporality**. This criterion implies that the cause of a disease must precede the development of the disease itself. This condition is fulfilled in infection models, where exposure to a single pathogen causes a specific disease and where the exposure always precedes the disease. In complex disease processes, detecting this condition is more challenging, as the exposures are often subclinical for a period of time and may not be the sole cause, but a contributory factor.
- **Biological gradient/dose–response relationship**. It stands to reason that if exposure to a risk factor, pathogen or condition causes or contributes to another disease, greater exposure should be linked to poorer outcomes of that disease.
- **Plausibility**. Fundamental to any step from association to causation is the ability to postulate the underlying biologically plausible mechanism, by which the causal relationship is expressed. In the absence of such an explanation, implying causality becomes challenging.
- **Coherence**. This criterion is an extension of the plausibility criterion, stating that the plausible explanation should fit with what is currently known of the biology of the disease. Again, not meeting this criterion is not necessarily a barrier to causality, as the knowledge base is subject to evolution and change.
- **Experiment**. Experimentally intervening to alter the exposure to an agent suspected of contributing to a disease, and then monitoring changes in the onset or progression of that disease further strengthens the causal hypothesis.
- **Analogy**. If the biological mechanism from one established causal relationship is accepted, other associations employing similar biological mechanisms have a lesser burden of proof before they are accepted as causal.

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework is another useful tool for rating the quality of evidence in systematic reviews and other evidence syntheses, but it can also be applied also to individual studies[14]. It provides a systematic approach and transparent tool for generating clinical practice recommendations. Evidence from randomised controlled trials (RCTs) begins as high-quality evidence but can be downgraded according to five factors: risk of bias, inconsistency, indirectness, imprecision and publication bias. Evidence from non-randomised studies begins as low-quality evidence, but its rating can be upgraded, if no other limitations have been identified, according to three reasons: large magnitude of effect, evidence of a dose–response effect and all plausible confounding taken into account. After the process of downgrading or upgrading, the quality of the evidence for each outcome is indicated as high, moderate, low or very low[15]. GRADE has adopted most of Bradford Hill's criteria, some implicitly, others explicitly. However, it has been proposed that GRADE should be adapted to consider the Bradford Hill criteria more extensively. The reason is that evidence from non-randomised studies may provide a more adequate or best available measure of a health-related research question, but that such evidence might be graded as lower quality in the GRADE framework[16].

The expert authors of the following book chapters have taken into account the above criteria for critically appraising the existing evidence on the associations or causal relationships between periodontitis and systemic diseases. This book therefore provides comprehensive, contemporary and well-considered insights into the clinical evidence and biological plausibility of each condition. This is underpinned by the body of scientific literature published to date, which has been critically discussed throughout the book. The reader will be provided with an understanding of how periodontitis impacts on the health of other organ systems and vice versa, but also of the limitations of existing studies and how these can be overcome in the future.

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Chapter 1

Periodontitis, obesity and diabetes mellitus

Bruno S. Herrera and Filippo Graziani

1.1 Introduction

In the last two decades, researchers have looked more deeply into the association of periodontitis and common major systemic chronic pathologies such as atherosclerosis[1], diabetes[2], obesity[3], and preterm labour[4] with adverse pregnancy outcomes[5]. The rationale of the periodontal-systemic link likely involves two important mechanisms: systemic inflammation and bacteraemia. One of the most important systemic diseases in this field is diabetes mellitus (DM). DM is a group of metabolic diseases characterised by hyperglycaemia due to decrease in insulin secretion, insulin response or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels[6]. The vast majority of cases of diabetes fall into two broad aetiopathogenetic categories: type 1 (T1DM) and 2 (T2DM). T1DM is the absolute deficiency of insulin secretion due to autoimmune beta-cell destruction in the pancreas. T2DM develops when there is an abnormally increased resistance to the action of insulin and the body cannot produce enough insulin to overcome the resistance[6,7].

1.1.1 Obesity

Overweight and obesity involve abnormal or excessive fat accumulation that may impair health and are considered major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and also periodontitis[8]. Childhood obesity results in the same conditions, with premature onset, or with greater likelihood of developing these diseases as adults. Thus, the economic and psychosocial costs of obesity alone, as well as when coupled with these comorbidities are striking[9]. According to the World Health Organization (WHO)[8], in 2016, more than 1.9 billion adults were overweight and, of these, over 650 million were obese. Worldwide obesity has nearly tripled since 1975 and most of the world's population live in countries where overweight and obesity kills more people than underweight. This epidemic is far from its resolution, since 41 million children under the age of 5 and over 340 million children and adolescents aged 5 to 19 were overweight or obese in 2016[8].

Body mass index (BMI, calculated as weight in kg/height in metres^2) provides the most useful population-level measure of overweight and obesity. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals. For adults, the WHO defines overweight as a BMI greater than or equal to 25; and obesity a BMI greater than or equal to 30[8]. Another way to assess this information is to use Z-scores (also known as standard deviation scores). It is obtained by dividing the median weight of the reference person or population by the standard deviation height or age of the reference population. Z-scores are sex-independent, thus permitting the evaluation of children's growth status by combining sex and age groups (Table 1-1). There are several factors that increase obesity risk, such as parental diet and/or obesity, a sedentary lifestyle, famine exposure, smoking, and alcohol binge drinking and regular high consumption, especially in women[9,13]. In addition, to date, over 60 relatively common genetic markers have been implicated in elevated susceptibility to obesity[9].

In the USA, a 2005 estimation indicated that obese men are thought to incur an additional US $1152 annually per person in medical spending, while obese women incur over double that. The authors estimate that around US $190 billion per year, approximately 21% of US health care expenditure, is due to treating obesity and obesity-related conditions[14]. In Europe, a 2008 review of 13 studies in 10 western European countries estimated the obesity-related health care burden had a relatively conservative upper limit of €10.4 billion annually[15,16].

1.1.2 Diabetes mellitus

Diabetes was first described in the Ebers Papyrus in 1500 BC, when it was called 'too great emptying of

Table 1-1 Common classifications of body weight in adults and children[9]

Age group		Age	Indicator	Normal weight	Overweight	Obese
Adults		≥ 20 y	BMI (kg/m²)	18.5–24.99	25.00 to 29.99	≥ 30.00
						Class 1: ≤ 34.99
						Class 2: ≤ 39.99
						Class 3: ≥ 40.00
Children	WHO Multicentre Growth Reference Study Group[10]	0–60 mo	BMI Z or WH Z	> −2 to ≤ 2 SD. At risk of overweight: > 1 to ≤ 2 SD	> 2 to ≤ 3 SD	> 3 SD
	de Onis et al[11] (WHO)	5–19 y	BMI Z	> −2 to ≤ 1 SD	1 to ≤ 2 SD	> 2 SD
	Kuczmarski et al[12] (CDC)	2–19 y	BMI percentile	≥ 5th to < 85th	≥ 85th to < 95th	≥ 95th

MI = body mass index; CDC = Centers for Disease Control and Prevention; SD = standard deviation of the optimum weight-for-height; WH = weight-for-height; WHO = World Health Organization; Z = Z-score.

the urine'. At the time, physicians from India observed that the urine from people with diabetes attracted ants and flies, calling it 'honey urine'. In 1776, the British physiologist Matthew Dobson first described that the sweet-tasting substance in the urine was sugar. However, it was only in the nineteenth century that glycosuria became an accepted diagnostic criterion for diabetes, after Michel Eugène Chevreul observed in 1815 that the sugar found in urine was glucose and after Hermann Von Fehling developed a quantitative test for glucose in urine in 1848[17]. Between 1893 and 1909, several researchers, including Paul Langerhans, observed that insulin deficiency was the factor responsible for the development of diabetes. Prior to its isolation and clinical use in 1922 by Frederick Banting and Charles Best, the only known treatment for diabetes was starvation diets, with not uncommonly death from starvation in some patients with diabetes T2DM[17]. Regarding oral hypoglycaemic agents, in 1918, C. K. Watanabe observed that guanidine caused hypoglycaemia[17]. Ten years later, biguanidine, a guanidine-modified molecule, was introduced for treatment of diabetes in Europe[17]. In 1949, Becton, Dickinson and Company began the production of a standardised insulin syringe designed and approved by the American Diabetes Association (ADA). The standardised syringe reduced dosing errors and the associated episodes of hyperglycaemia and hypoglycaemia.

Diabetes impacts more than 415 million people worldwide and two thirds of people with diabetes die of heart disease and stroke[18]. In addition, the risk for cardiovascular disease mortality is two to four times higher in people with diabetes than in people who do not have diabetes[7]. Diabetes is a disease that rarely occurs alone. When it is combined with abdominal obesity, high cholesterol and/or high blood pressure, it becomes a cluster of the highest risk factors of heart attack. The combination of these diseases is termed metabolic syndrome (MS), also known as insulin-resistance syndrome or cardiometabolic syndrome. According to the most recent guidelines issued in 2009 by the International Diabetes Federation (IDF), American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI), MS is defined as the combination of at least three of the following con-

ditions: increased plasma glucose (≥ 100 mg/dl), hypertension (≥ 130/85 mmHg or systemic arterial hypertension treatment), hypertriglyceridaemia (≥ 150 mg/dl), low high-density level cholesterol (HDL, < 40 mg/dl) and/or elevated abdominal circumference (≥ 94 cm + ethnicity-specific values)[19].

MS is a major public health challenge worldwide since it is associated with a five-fold elevated risk of T2DM and a two- to three-fold risk of cardiovascular disease[20]. MS predicts diabetes independently of other factors. However, obesity worsens the diabetes risk associated with MS or impaired glucose tolerance, due to its relation to insulin resistance and due to being the central element of MS[21]. Data from the third National Health and Nutrition Examination Survey (NHANES III) in adults aged 50 years or older indicated that the prevalence of coronary heart disease was greatest in individuals with MS and DM combined[22].

Circulating blood glucose binds to, and therefore glycates, the red blood cell protein haemoglobin. This glycation occurs proportionally to the blood glucose concentration. By measuring the percentage of glycated haemoglobin (HbA1c) in the blood, the average blood glucose over the past 2 to 3 months and a person's success in controlling their blood glucose can be estimated[23].

According to the position statement published by the ADA in 2018[24], it is suggested that the HbA1c should be less than 7% for non-pregnant adults, which is an average glucose concentration of 154 mg/dl or 8.6 mmol/l (Table 1-2). However, it can be less stringent; for example, in patients with a history of severe hypoglycaemia, long-standing diabetes and limited life expectancy, < 8% is acceptable. The HbA1c test should be conducted at least two times per year in patients who are meeting the treatment goals and who have stable glycaemic control, and quarterly in patients whose therapy has changed or who are not meeting glycaemic goals[24].

Diabetes and its complications are a major cause of morbidity and mortality worldwide and contribute substantially to health care costs. The major

Table 1-2 The relationship between haemoglobin A1c (A1C) and estimated average glucose (eAG, calculated by the formula eAG = 28.7 × A1c − 46.7)

A1C	eAG	
%	mg/dl	mmol/l
6.0	126	7.0
6.5	140	7.8
7.0	154	8.6
7.5	169	9.4
8.0	183	10.1
8.5	197	10.9
9.0	212	11.8
9.5	226	12.6
10.0	240	13.4

complications of DM are divided into: microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (cardiovascular diseases and lower-extremity amputation). It has been proposed by Loe[25] that periodontitis would be the sixth complication of diabetes. According to the Consensus Report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions[26], there are no characteristic phenotypical features that are unique to periodontitis in patients with DM, so the level of glycaemic control in diabetes influences the grading of periodontitis and it should be included in a clinical diagnosis of periodontitis as a descriptor. In addition, most of the evidence for its adverse effects on periodontal tissues is from patients with T2DM. However, the level of hyperglycaemia over time, irrespective of the type of diabetes, is of importance when it comes to the magnitude of its effect on the course of periodontitis[26]. Therefore, the aim of this chapter is to discuss the evidence for the bidirectional association, epidemiology and mechanisms linking periodontitis, obesity and DM.

SUMMARY

- Worldwide, more than 1.9 billion adults are overweight and, of these, over 650 million are obese.
- Overweight and obesity have genetic, behavioural, socio-economic and environmental origins.
- Paradoxically, coexisting with undernutrition, an escalating global epidemic of obesity – also known as 'globesity' – is taking over many parts of the world.

Annually, the cost of globesity is around US $190 billion per year in the USA and €10.4 billion in Europe.

1.2 Clinical evidence

1.2.1 Periodontitis and obesity

The association between obesity and periodontitis was first reported in 1977, when changes in the periodontium of obese rats was found[27]. The first human study reporting this relationship was conducted by Saito et al[28]. In this study, the periodontal status of 241 healthy Japanese subjects was assessed. The authors observed that the relative risk of periodontitis was 3.4 in subjects with BMIs of 25.0 to 29.9 kg/m^2, and 8.6 in those with BMIs of ≥ 30 kg/m^2, compared with subjects with BMIs of < 20 kg/m^2 [28]. Since then, some systematic and non-systematic reviews have been published regarding this association. However, the level of evidence is low, as they include mainly cross-sectional studies, whilst prospective evidence is scarce[29]. In addition, there are several confounding factors related to obesity that should be clarified to elucidate the direction of this association. In a systematic review, Moura-Grec et al[30] found an association between periodontitis and obesity in 17 studies, a trend in 8 studies, and no association in 6 studies. When they compared normal weight, overweight and obesity, they observed an odds ratio (OR) of 1.30 (95% confidence interval [CI] 1.25 to 1.35) of the risk to have periodontitis in an obese subject. Data from a systematic review by Keller et al[29] including interventional and longitudinal studies showed that overweight[31], obesity[31,32], weight gain[32] and increased waist ratio[27,28] are risk factors directly associated with developing or worsening periodontitis.

Jimenez et al[31] examined the association between measures of adiposity and self-reported periodontitis, using data from more than 36,000 healthy male participants of the Health Professionals Follow-Up Study, who were periodontally healthy at baseline and were followed for more than 20 years. They observed that overweight and obesity increase the risks of having periodontitis (hazard ratio [HR] 1.09, 95% CI 1.01 to 1.17, and HR 1.30, 95% CI 1.16 to 1.45, respectively). When the obesity data was broken down among dental and non-dental professionals, they only observed a significant association in the first group (HR 1.52, 95% CI 1.32 to 1.75 vs. HR 1.07, 95% CI 0.90 to 1.27). Regarding the waist ratio, subjects with more than 40.25 inches in waist circumference exhibited a 25% (95% CI 1.09 to 1.44) increased risk of periodontal disease compared with men with less than 40.25 inches. All data were adjusted by age, number of teeth at baseline, physical activity or fruit and vegetable intake. It is important to highlight that periodontitis was self-reported in this study, thus the lack of an expert diagnosis is likely to introduce some errors and biases in the study outcomes.

Gorman et al[32] found that a 1% increment in waist-to-height ratio was associated with a 3% increase in the HR of having periodontitis progression over 27 years, and an augmentation of 1 cm in

waist circumference was associated with a 1% to 2% increase in the hazard of periodontitis in 1038 white males. Obese subjects had an HR of 1.52 (95% CI 1.05 to 2.21) for having clinical attachment loss greater than 5 mm and an HR of 1.60 (95% CI 1.07 to 2.38) of having alveolar bone loss greater than 40% of more than two teeth when compared to normal weight counterparts. Furthermore, treatment outcomes may be diminished by obesity: Martinez-Herrera et al[33] reported, in their systematic review, that obesity had an impact on the outcome of scaling and root planing in patients with periodontitis in three of the 28 studies included. On the other hand, six studies did not show this impact. Conclusions are difficult to draw because of the high methodological heterogeneity in terms of evaluation of the periodontitis outcome measures used, risk factors analysed, and age and gender of the participants in the different studies. In a cross-sectional study published by the same group, the authors observed that periodontitis was more prevalent in obese subjects (80.9% vs. lean 41.2%), with a six-fold increased risk of having periodontitis. In addition, obese subjects displayed higher diastolic blood pressure, increased circulating tumour necrosis factor alpha (TNF-α) and high-sensitivity C-reactive protein (hsCRP), as well as lower high-density lipoprotein (HDL) than lean subjects. Interestingly, obese subjects with insulin resistance had higher systolic blood pressure, higher glucose, insulin, HbA1c and triglyceride levels, more insulin resistance (HOMA-IR [homeostatic model assessment of insulin resistance]), and a higher number of teeth with probing depths greater than 4 mm than those obese subjects without insulin resistance[34].

D'Aiuto et al[35] analysed data from almost 14,000 men and women from the third NHANES in the United States and observed that subjects older than 45 years with severe periodontitis were 2.31 times more likely to have metabolic syndrome, defined by concurrence of hypertension, atherogenic lipid profiles, obesity and insulin resistance; compared to unaffected individuals after adjusting for confounders. Furthermore, diagnosis of metabolic syndrome increased by 1.12 times per 10% increase in gingival bleeding and 1.13 times per 10% increase in the proportion of periodontal pockets. Morita et al[36] followed up more than 3000 Japanese workers for 5 years and assessed the incidence of periodontitis. They observed a significant association between BMI and the development of periodontal pockets of greater than 4 mm, and the hazard ratios for women were higher than they were for men. However, this study used partial-mouth recording and the Community Periodontal Index to assess periodontal status, which would underestimate the true periodontal status. Merchant et al[37] observed in 39,461 males that individuals who maintained a normal weight, pursued regular exercise, and consumed a diet in conformity with the Dietary Guidelines for Americans and the Food Guide Pyramid recommendations, were 40% less likely to have periodontitis.

In addition, periodontal pathogen populations seem to be altered in obese subjects. For example, Haffajee and Socransky[38] observed an overgrowth of *Tannerella forsythia* in the biofilms of periodontally healthy obese individuals that might put them at risk for initiation of periodontitis. They also observed that the ORs of overweight and obese subjects exhibiting periodontitis were 3.1 (95% CI 1.9 to 4.8) and 5.3 (95% CI 2.8 to 9.5), respectively, when compared with subjects with normal BMI. Logistic regression analysis indicated an OR of 2.3 (95% CI 1.2 to 4.5) for an obese subject to exhibit periodontitis after adjusting for age, gender and smoking status. In a recent study, Maciel et al[39] observed that obese male subjects with periodontitis harboured higher levels and/or higher proportions of periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans, Eubacterium nodatum, Fusobacterium nucleatum subspecies vincentii, Parvimonas micra, Prevotella intermedia, T. forsythia, Prevotella melaninogenica* and *Treponema socranskii* when compared to normal weight subjects with periodontitis. Furthermore, the healthy sites of the obese subjects also exhibited higher proportions of some of the pathogens than the normal weight counterparts[39].

In terms of treatment outcome, Suvan et al[40] investigated the predictive role of overweight/obesity on clinical response following non-surgical periodontal therapy in 260 adults. On re-evaluation, i.e., after 8 weeks, they observed that obesity was an independent predictor of poorer periodontal treatment outcomes. These patients had, on average, 3.2% (95% CI 0.7% to 5.6%) more sites with probing depths greater than 4 mm when compared with normal weight subjects after adjustment for the baseline. For every BMI increase of 10 kg/m^2, the mean percentage of sites with probing depths greater than 4 mm increased by 2.5% (95% CI 1.10% to 3.80%). No differences were found in bleeding on probing. It is worth pointing out that the magnitude of this association was similar to that of smoking, which was also linked to a worse clinical periodontal outcome[40]. However, Palomo[41] stated that this study had limitations inherent in the study design. The confounders for periodontitis, such as smoking and diabetes, were not part of the exclusion criteria. Instead, statistical analysis was undertaken to account for them, increasing the risk for false-positive associations. Thus, a poor outcome after periodontal therapy in the obese patients of this study may in fact not be fully attributed to the BMI alone[41].

It is difficult and complex to unravel the relative contributions of obesity and metabolic status, including hyperglycaemia, to periodontitis. Positive association between obesity and periodontitis has been consistently shown in recent meta-analyses. However, few of them have a prospective or a longitudinal design, and these relationships appear to be modest[26]. Taken together, there is significant evidence of an association between overweight/obesity and the prevalence, extent and severity of periodontitis, as well as periodontal treatment outcomes in children, adolescents and adults. However, the magnitude and mechanisms of this association require further clarification. The available evidence comes mainly from cross-sectional, experimental and longitudinal studies, respectively[33,42]. The difficulty to reach a final conclusion is related to the difficulty to evaluate the mechanisms underlying the association between them, because most of the studies involved a cross-sectional design. In addition, there is heterogeneity in the definition of obesity in most of the studies, which evaluate the degree of obesity by calculating BMI, however some of them also include wait-circumference, waist-hip ratio and, in some cases, percentage body fat. In order to confirm the causal relationship and the pathophysiological mechanism involved in the association between obesity and periodontitis, further prospective studies are needed[33,42].

SUMMARY

- A potential association between obesity and periodontitis was first reported in 1977.
- There are several confounding and risk factors related to obesity that should be adjusted for in future studies and biologically clarified to elucidate the association between obesity and periodontitis.
- Data from NHANES show that subjects older were 2.31 times more likely to have metabolic syndrome.
- 1% increment in waist-to-height ratio was associated with a 3% increase in the hazard of having periodontitis progression in a 2012 study.
- The overall level of evidence is low; therefore, an association cannot yet be confirmed.

1.2.2 Periodontitis and DM

Diabetes is one of the largest global health emergencies of the 21st century. In 2015, the International Diabetes Federation estimated that 415 million people worldwide have diabetes[43]. Despite better awareness and new developments in the treatment of diabetes and prevention, an unrelenting increase has been observed in the number of people with the disease. By 2040, an increase to 642 million is expected, where a major concern is low- and middle-income countries and in those countries that have experienced rapid economic growth[44]. The number could be higher, since there are numerous people from many countries that have the disease undiagnosed (especially in Africa, where it is estimated that more than 65% of individuals with diabetes remain undiagnosed)[45].

The percentage of adults with diabetes increased with age, reaching a high of 25.2% among those aged 65 years or older[46]. The age-adjusted prevalence of diagnosed and undiagnosed diabetes is higher among Asians, non-Hispanic blacks, and Hispanics, respectively[46]. According to the ADA, the estimated costs associated with diabetes in the United States in 2002 totalled US $132 billion, with direct medical costs of US $92 billion and indirect costs (disability, loss in work productivity and premature mortality) of US $40 billion[47]. T1DM, previously referred to insulin-dependent diabetes or juvenile-onset diabetes, results from a cell-mediated autoimmune destruction of the insulin-producing pancreatic beta cells. It accounts for only 5% to 10% of those with diabetes[6] and its prevalence increases at a rate of approximately 3% per year globally[43]. It frequently occurs in childhood; however, 84% of people living with T1DM are adults. It affects both genders equally[46] and decreases life expectancy by an estimated 13 years[48].

For over 70 years, researchers have been trying to understand the relationship between diabetes and periodontal diseases. The first study describing this relationship was published by Williams and Mahan[49], who found that patients with poorly controlled diabetes required less insulin after treatment of periodontal infection with extractions and antibiotics. Years later, Grossi and Genco[50] postulated a 'self-feeding two-way system of catabolic response resulting in more severe periodontitis and increased difficulty controlling blood sugar'.

1.2.2.1 Pathogenesis of DM

T1DM

T1DM is a disorder that arises following the autoimmune destruction of insulin-producing pancreatic beta cells, characterised histologically by insulitis (i.e., islet cell inflammation) and associated beta-cell damage. The disease is most often diagnosed in children and adolescents presenting with a classic trio of symptoms (polydipsia, polyphagia, polyuria) alongside hyperglycaemia[51]. Many different theories have been postulated to explain its development, including molecular mimicry leading to the generation of an autoimmune response, alteration of self-antigens to a now antigenic self, defective major histocompatibility complex (MHC) expression on cells of the immune system, breakdown in central tolerance, deleterious trafficking of dendritic cells from beta cells to pancreatic lymph nodes, sensitivity of the beta cells to free radical or cytokine-induced damage local viral infection and defects in peripheral immune tolerance[52] (Table 1-3).

T2DM

T2DM, previously referred to as non-insulin-dependent diabetes, or adult-onset diabetes, develops when beta cells fail to secrete sufficient insulin to keep up with the demand, usually in the context of increased insulin resistance[53]. The development of T2DM is caused by a combination of lifestyle and genetic factors. Some of these factors can be controlled, such as diet and obesity, and other factors cannot, such as increasing age, female gender and genetics. Most patients with this form of diabetes are obese and weight loss improves insulin sensitivity in liver and skeletal muscle tissues. Genome-wide association studies have identified more than 130 genetic variants associated with T2DM, glucose lev-

Table 1-3 T1DM vs. T2DM

T1DM	T2DM
Autoimmune destruction of pancreatic beta cells	Over time, insulin receptors become less sensitive/insulin resistance – beta cells deteriorate over time
Children/teenagers are mostly affected	Adults, elderly and certain ethnic groups (African-American, Hispanic, Native American, Pacific Islander groups) are mostly affected
Lack of insulin	Obesity as risk factor
About 5% of all diabetes cases	About 95% of all diabetes cases
Involvement of kidneys, eyes and heart	Involvement of kidneys, eyes and heart
Diet and exercise cannot reverse the condition	Diet and exercise can reverse the condition
Extrinsic insulin requirement	Oral medication, insulin may be required

T1DM: type-1 diabetes mellitus; T2DM: type-2 diabetes mellitus

els or insulin levels; however, these variants explain less than 15% of disease heritability[54,55]. The lifetime risk of developing T2DM is about 40% if one parent has T2DM and higher if the mother has the disease[56]. In comparison, the risk for T1DM is about 5% if a parent has T1DM and higher if the father has the disease[57] (Table 1-3).

1.2.2.2 Interventional studies on the impact of glycaemic control upon complications of diabetes

Large clinical trials demonstrated the need of the glycaemic control to avoid systemic-related complications of diabetes. The Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) were conducted in 29 medical centres in the United States and Canada. They included 1441 volunteers aged 13 to 39 years with T1DM, monitored from 1982 to 1993 (DCCT) and from 1994 to 2014 (EDIC), with a mean follow-up period of 6.5 years, and assessed the incidence and predictors of cardiovascular disease events such as heart attack or stroke, as well as diabetes complications related to the eye, kidney and nervous system. In the DCCT study, the patients were randomised to either receive intensive therapy (at least three insulin injections per day or continuous subcutaneous insulin infusion with external pumps) in order to maintain safe asymptomatic glucose control (with a target of pre-meal glucose level between 70 and 120 md/dl and post-meal glucose levels less than 180 mg/dl) or conventional control (one to two insulin injections per day). The average blood glucose was 155 mg/dl in the intense control group and 231 mg/dl in the conventional group. It was observed that HbA1c in the intensively controlled group was 2% lower than in the control group, with a 76% reduction in retinopathy, 34% in the development of early nephropathy and 69% in the development of neuropathy[58]. EDIC also observed that there was a reduction in cardiovascular events and death from cardiovascular disease when intense treatment in the previously conventionally controlled diabetes is provided[59].

In another large randomised controlled trial, The United Kingdom Prospective Diabetes Study (UKPDS), 5102 patients with newly diagnosed

T2DM in 23 centres within the UK were studied between 1977 and 1991. Patients were followed for an average of 10 years. Intensive therapy (insulin or oral agents) was compared to conventional therapy (diet with or without pharmacological therapy). This study provided strong evidence that intense glycaemic control in T2DM (median HbA1c of 7.0% vs. 7.9%) can decrease the morbidity and mortality of the disease by decreasing its chronic complications. As observed in T1DM clinical trials, such as DCCT and EDIC, lowering blood glucose levels decreases retinopathy, nephropathy and possibly neuropathy, showing that hyperglycaemia is the cause of, or at least the major contributor to these complications. In addition, the epidemiological analysis of the UKPDS data showed that for every percentage point decrease in HbA1c, there was a 35% reduction in the risk of microvascular complications, 25% in diabetes-related deaths, a 7% reduction in all-cause mortality, and 18% in myocardial infarction. Importantly, there is no glycaemic threshold for these complications above normal glucose levels[60,61]. Taken together, DCCT and UKPDS, along with other studies, demonstrate that glycaemic control is the key factor to control systemic complications related to DM.

1.2.2.3 Association between periodontitis and DM

The relationship between periodontitis and diabetes has been a subject of several longitudinal and interventional studies and it has been suggested that their relationship is bidirectional in both T1DM and T2DM and periodontal diseases[62]. For example, in diabetes, local inflammatory reactions within the periodontal tissues are modulated by the associated metabolic dysregulation (i.e. tissue responses to inflammatory stimuli are enhanced in poorly controlled diabetes)[63], which is explained in further detail in Section 1.3 'Cellular and molecular mechanisms'.

Epidemiological studies

Diabetes and periodontitis are chronic inflammatory diseases that have been considered to be biologically linked. Diabetes is known to be a primary risk factor for periodontitis, and periodontitis is considered as the sixth complication of DM[25]. Evidence linking periodontitis and diabetes began to emerge in the 1990s from several studies conducted in the Pima Indian population in the United States[64]. Cross-sectional studies showing the prevalence and longitudinal studies showing the incidence of dia-

SUMMARY

- In 2015, it was estimated that 415 million people worldwide have diabetes.
- By 2040, an increase to 642 million is expected.
- The estimated costs associated with diabetes in the United States in 2002 were US $132 billion.
- Intense glycaemic control in both T1DM and T2DM can decrease the morbidity and mortality.
- For every percentage point decrease in HbA1c, there are:
  - 35% reduction in the risk of microvascular complications,
  - 25% reduction in diabetes-related deaths,
  - 7% reduction in all-cause mortality,
  - 18% reduction in combined fatal and nonfatal myocardial infarction.

betes, demonstrate that periodontitis is significantly more abundant in subjects who have T1DM[65] or T2DM[66] diabetes, with a higher risk of having the severe forms of periodontitis. The risk of periodontitis is approximately three to four times higher in people with T2DM than in non-diabetes subjects[67]. The direct relationship between the glucose level and the severity of periodontitis has been demonstrated, with the ORs in T2DM patients of periodontal destruction being 1.97 in well, 2.10 in moderately, and 2.42 in people with poorly controlled diabetes[68]. In addition, data from the NHANES show that individuals with diabetes are at greater risk for incident and prevalent periodontitis and have more severe periodontitis than individuals without diabetes, after controlling for age, education, smoking status and calculus[69]. These data were also supported by a recent meta-regression analysis of longitudinal studies, which included 13 studies. The authors reported that diabetic subjects present a 70% higher incidence or progression risk of periodontitis than non-diabetics (relative risk [RR] 1.86, 95% CI 1.3 to 2.8), despite of high heterogeneity between studies[70]. Similarly, a 2019 Taiwanese large-scale cohort study, including 39,384 patients with new-onset diabetes and 39,384 subjects without periodontitis, found that patients with diabetes had a higher risk for periodontitis compared with the patients without diabetes (adjusted hazard ratio 1.04, 95% CI 1.01 to 1.08). As a major shortcoming, however, periodontitis was poorly defined, using ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes only[71]. Conversely, a systematic review and meta-analysis of 12 intervention studies (follow-up period: 6 months) published in the same year, stated that there was no significant difference in pocket reduction or clinical attachment gain between periodontitis patients and those with both diabetes and periodontitis. Furthermore the level of HbA1c at baseline did not affect the difference in pocket reduction. However, this study pooled data from smokers and non-smokers, which is likely to have affected treatment outcomes and therefore the results of this meta-analysis. Furthermore, heterogeneity of the included studies with regard to periodontal diagnosing as well as the relatively short follow-up period may have impacted the results[72].

On the other hand, there is evidence for periodontitis promoting the development of diabetes. Overall, six studies with a total sample of 77,716 participants from the United States, Japan and Taiwan demonstrated that patients with periodontitis exhibit a higher chance of developing pre-diabetes and diabetes[2]. One of these studies demonstrated that systemically healthy subjects with probing depths equal to or greater than 6 mm have a 3.45 times higher risk of developing diabetes than those without periodontitis[73]. Another study demonstrated that subjects with gingivitis have a 40% elevated risk, subjects with periodontitis a 50% elevated risk, and subjects who are partially edentulous a 70% elevated risk of developing T2DM. It is important to mention that this association was observed in non-smoking subjects with normal weight[74]. This association can also be seen for gestational DM[75]. Furthermore, a recent (2019) study was conducted in 139 periodontitis patients, which employed chair-side screening for HbA1c levels and considered BMI, waist circumference and periodontal parameters. It was found that almost 25% of the subjects had unknown hyperglycaemia and those with HbA1c ≥ 5.7% displayed higher proportions of sites with clinical attachment loss > 5 mm[76].

One recently published longitudinal study followed 2047 subjects aged 20 to 81 years from the Study of Health in Pomerania cohort over a period of 11 years. Although the study was well conducted and excluded many potential biases, it reported no association between periodontal parameters and either diabetes incidence or long-term changes in HbA1c. One shortcoming of this study may be, however, that diabetes was assessed by different methods (self-reporting or antidiabetic medication intake or HbA1c levels or fasting blood glucose)[77].

Moreover, the majority of the studies report an association between worse periodontal conditions and diabetes complications. For example, Shultis

et al[78] observed that moderate and severe periodontitis, as well as edentulousness, significantly predicted both macroalbuminuria (2.0, 2.1 and 2.6 times higher, respectively) and end-stage renal disease in a dose-dependent manner among Pima Indians with T2DM. In this population, as shown by another study, those with severe periodontitis had a 3.5 times higher risk for cardiorenal death; moreover, nephropathy and death from ischaemic heart disease were significantly predicted by periodontitis[79]. In a systematic review and meta-analysis of 27 epidemiological studies, Ziukaite et al[80] observed that the prevalence of diabetes was 13.1% among subjects with periodontitis and 9.6% among subjects without periodontitis. Interestingly, for subjects with periodontitis, the prevalence of diabetes was 6.2% when diabetes was self-reported, compared to 17.3% when diabetes was clinically assessed. According to this study, the highest prevalence of diabetes among subjects with periodontitis was observed in studies originating from Asian countries (17.2%) and the lowest in studies describing populations from Europe (4.3%). The overall OR for patients with diabetes among those with periodontitis was 2.27, compared to those without periodontitis. However, there was a substantial variability in the definitions of periodontitis, a combination of self-reported and clinically assessed diabetes, and a lack of assessment of confounding for diabetes in the included studies, introducing estimation bias[80].

Nevertheless, according to Graziani et al[2], periodontitis has an impact on diabetes control, including its incidence and complications. Poor glycaemic control and a higher risk of developing diabetes are observed in systemically healthy individuals with periodontitis. Diabetic individuals with periodontitis demonstrate a worsening of glycaemic control and significantly higher prevalence of diabetes-related complications. For example, patients with T2DM and comorbid periodontitis have significantly more cardiorenal complications (OR 3.5, 95% CI 1.2 to 10.0)[81], neuropathic foot ulcerations (OR 6.6, 95% CI 2.3 to 18.8)[82], cardiovascular complications (OR 2.6, 95% CI 1.6 to 4.2)[83] and overall mortality (RR 1.51, 95% CI 1.11 to 2.04 for each 20% increment in mean whole-mouth alveolar bone loss)[84]. However, the studies suffered from intrinsic limitations that render the overall applicability of the results weak. For example, some of the evidence was indirectly drawn from manuscripts that did not have the primary intention of assessing the effect of periodontitis on glycaemic control. In addition, there is heterogeneity in terms of adjustment of confounders as well as of the definitions of periodontitis. Furthermore, the possibilities of selective data reporting and publication bias cannot be excluded[2].

Taken together, there is strong and significant evidence that DM has an impact on the prevalence and severity of periodontitis. This evidence has evolved from surveys, case-control studies, narrative reviews and systematic reviews, but mainly from epidemiological studies. The association appears to be similar in T1DM and T2DM; however, the available evidence is focused particularly on T2DM. There is little evidence that the clinical features of periodontitis in patients with DM differ from those without DM. Regarding the impact of periodontitis on DM, there is accumulating evidence that periodontitis contributes to the onset and persistence of hyperglycaemia, poorer glycaemic control in individuals with DM, and an increase in DM incidence[85,86].

Interventional studies

Consequently, if periodontitis has a role in diabetes, it would be logical to infer that periodontal therapy impacts circulating levels of inflammatory cytokines, adiponectin, insulin resistance and glycaemic control. Efforts have been made to understand the impact of periodontal therapy in diabetes control. It has been shown that periodontal treatment can improve glycaemic control, lipid profile and insulin resistance, reduce serum inflammatory cytokine levels and increase serum adiponectin levels in T2DM patients[87]. Sun et al[87] studied 190 moderately to poorly controlled T2DM patients (HbA1c

between 7.5% and 9.5%) with periodontitis. They observed that after 3 months of periodontal therapy, the serum levels of C-reactive protein, TNF-α, interleukin (IL)-6, fasting plasma glucose, HbA1c, fasting insulin and the HOMA-IR index decreased, the latter being a method for assessing insulin resistance from fasting blood glucose and insulin concentrations. Adiponectin was significantly increased in the treated group compared to the non-treated group[87].

The positive impact of a non-surgical periodontal therapy on HbA1c was also observed in a recent study by D'Aiuto et al[88]. In this 12-month randomised clinical trial, 264 subjects were allocated to receive intensive periodontal treatment (IPT; whole mouth subgingival scaling, surgical periodontal therapy and supportive periodontal therapy every 3 months until completion of the study) or control periodontal treatment (CPT; supragingival scaling and polishing at the same time-points as in the IPT group). They observed that HbA1c was 0.6% (95% CI 0.3% to 0.9%) lower in the IPT group than in the CPT group after 12 months, with adjustment for baseline HbA1c, age, sex, ethnicity, smoking status, duration of diabetes and BMI[88]. The question that still remains is whether the observed benefits are sustained beyond 12 months.

The impact of periodontal treatment is largely witnessed by the systematic reviews on this topic. Engebretson and Kocher[89] demonstrated in a meta-analysis that periodontal therapy significantly reduced HbA1c 3 to 4 months post-treatment, ranging from 0.27% to 1.03% (95% CI −0.54 to −0.19). In the latest update, Madianos and Koromantzos[90] confirmed that non-surgical periodontal therapy reduced HbA1c in patients with diabetes. They observed that there was a reduction 3 to 4 months post-treatment, ranging from −0.27% (95% CI −0.46 to −0.07) to −1.03% (95% CI 0.36 to −1.70) and at 6 months post-treatment, the HbA1c reduction ranged from −0.02 (95% CI −0.20 to −0.16) to −1.18% (95% CI −0.72 to −1.64). The data derived from the meta-analysis clearly indicate the positive effect of periodontal decontamination on glycaemic control. It is important to highlight that this effect cannot be underestimated since, as shown before, for every percentage point decrease in HbA1c, there is a 35% reduction in the risk of microvascular complications, 25% reduction in diabetes-related deaths, a 7% reduction in all-cause mortality, and an 18% reduction in combined fatal and nonfatal myocardial infarction. This further reinforces the hypothesis of a link between periodontitis and diabetes[90].

Conversely, in a multicentre, randomised clinical trial, Engebretson et al[91] observed that non-surgical periodontal therapy did not improve glycaemic control in patients with T2DM. However, several authors indicate that the periodontal therapy provided in this study failed to clinically manage the periodontal infection, since the subjects still had high residual plaque levels (72%) and bleeding scores (42%) after the therapy. In addition, the mean HbA1c value at baseline was close to the therapeutic target, thus, a substantial improvement of the HbA1c by periodontal intervention could not be expected. Lastly, the subjects from the treatment group were obese (mean BMI 34.7), which would probably have masked any anti-inflammatory effect of successful periodontal treatment[92].

The controversy regarding the effect of periodontal treatment on glycaemic control may be related to the heterogeneity of the trial designs. These are, for example, non-surgical vs. surgical periodontal therapy provided, the periodontal treatment outcomes assessed, the periodontitis definition used (severity vs. extent vs. both), the selection criteria for the type of DM (T1DM vs. T2DM vs. both), the variability in the range of levels of glycated haemoglobin, and the follow-up periods, where periods of 3 months to assess HbA1c changes may be considered too short[23,86]. Table 1-4 lists the most important interventional studies. It presents the effect of periodontal treatment on glycaemic control of T1DM and T2DM. Table 1-5 gives an overview of clinical studies investigating the association between periodontitis and T1DM.

The association between periodontitis and systemic diseases has become a hot topic in recent years. This comprehensive book reviews the clinical evidence and biological plausibility of the many systemic diseases that have been linked to periodontitis. Edited by Dr Josefine Hirschfeld and Prof Iain L.C. Chapple, experts in each field discuss the mechanisms at work, citing the available key literature and clearly summarising current knowledge and understanding of the associations between periodontitis and diabetes mellitus, cardiovascular diseases, chronic kidney disease, inflammatory bowel diseases, rheumatoid arthritis, respiratory diseases, pregnancy and fertility, malignancy, neurodegenerative diseases, stress and depression, and autoimmunity. Each chapter critically appraises the existing evidence, providing comprehensive, contemporary and well-considered insights into the clinical evidence and biological plausibility of each condition, as well as the limitations of existing studies and how these can be overcome in the future. Periodontitis and Systemic Diseases: Clinical Evidence and Biological Plausibility is an indispensable reference for both clinicians and researchers.

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