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REVIEW

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Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doctors (WONCA Europe)

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Abstract

Aim: To explore the implications for dentists and family doctors of the association between periodontal and systemic diseases and the role of dentists and family

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doctors in managing non-communicable diseases (NCDs) and promoting healthy lifestyles.

Materials and Methods: The consensus reports of the previous Focused Workshops on the associations between periodontitis and diabetes (2017) and periodontitis and cardiovascular diseases (2019) formed the technical reviews to underpin discussions on both topics. For the association with respiratory diseases, a systematic review was specifically commissioned for the Workshop discussions. Working groups prepared proposals independently, and then the proposals were discussed and approved at plenary meetings.

Results: Periodontitis is independently associated with cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea and COVID-19 complications. Dentists and family doctors should collaborate in managing NCDs, implementing strategies for early detection of periodontitis in primary care centres and of cardiovascular diseases or diabetes in dental settings. Family doctors should be informed about periodontal diseases and their consequences, and oral health professionals (OHPs) should be informed about the relevance of NCDs and the associated risk factors.

Conclusions: Closer collaboration between OHPs and family doctors is important in the early detection and management of NCDs and in promoting healthy lifestyles. Pathways for early case detection of periodontitis in family medicine practices and of NCDs in dental practices should be developed and evaluated.

KEYWORDS
cardiovascular diseases, diabetes, family doctors, periodontitis, respiratory diseases

Clinical Relevance

Scientific rationale for study: Closer collaboration between oral health professionals (OHPs) and family doctors is important in the early case detection and management of non-communicable diseases (NCDs) (including cardiovascular diseases, diabetes, respiratory diseases and periodontitis) and in promoting healthy lifestyles.

Principal findings: Periodontitis is independently associated with cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, obstructive sleep apnea and COVID-19-associated complications, and treatment of periodontitis is associated with improvements of systemic health.

Practical implications: Strategies for early case detection/prevention of NCDs, including periodontitis, should be developed for family doctors, OHPs and healthcare funders. Evidence-based information on the reported associations between periodontitis and other NCDs should be made available to family doctors, OHPs, healthcare funders, patients and the general population.

1 | INTRODUCTION

Periodontitis is characterized by the progressive destruction of the tooth-supporting apparatus (periodontium), with primary features being clinical attachment and alveolar bone loss, presence of periodontal pockets and bleeding on probing (Papapanou et al., 2018). It is initiated by the accumulation of bacterial biofilms at and below the gingival margin, which activates the host immune–inflammatory response. The latter drives dysbiosis within the oral biofilm, which triggers a dysregulation of immune–inflammatory processes (Meyle & Chapple, 2015) and ultimately results in the destruction of the periodontal tissue (Hajishengallis & Chavakis, 2021).

Periodontitis is a major public health problem because of its high prevalence, being the most common chronic inflammatory non-

communicable disease (NCD) of humans. According to data originating from the Global Burden of Disease (GBD) database, 1.1 billion cases of severe periodontitis were present globally in 2019, and an 8.44% (95% confidence interval [CI]: 6.62%–10.59%) increase in age-standardized prevalence rate of severe periodontitis was observed between 1990 and 2019 (Chen et al., 2021). Periodontitis also presents a major public health burden because of its associated morbidity, leading to disability due to impaired masticatory function, speech and aesthetics or edentulism. It is a source of social inequality, significantly impairs quality of life, has a negative impact on general health and is associated with significant dental and medical care costs (Tonetti et al., 2017).

Periodontitis has been associated with a range of systemic diseases including diabetes (Sanz et al., 2018a, 2018b), cardiovascular diseases (CVDs; Sanz, Del Castillo, et al., 2020; Sanz, Marco Del Castillo, et al., 2020) and respiratory diseases. It is also independently associated with premature death from all causes or from CVDs (Garcia et al., 1998; Linden et al., 2012; Soder et al., 2007), in particular in multi-morbid populations, where the impact of periodontitis is equivalent to having co-morbid diabetes mellitus (Sharma et al., 2016). Periodontitis also results in increased medical expenditure (Sato et al., 2016).

Diabetes is a highly prevalent NCD, with a global prevalence estimated at 9.3% (463 million people), and expected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi et al., 2019). Type 2 diabetes is a major cause of disability and premature mortality, mainly from vascular and renal complications (Tuomi et al., 2014). The reported bidirectional association with periodontitis was jointly explored in the Focused Workshop of the European Federation of Periodontology (EFP) and the International Diabetes Federation (IDF) in 2017 (Sanz et al., 2018a, 2018b).

CVDs comprise a large and diverse group of different pathologies, including ischemic heart disease, stroke, hypertension, rheumatic heart disease, cardio-myopathies and atrial fibrillation. CVDs are the leading cause of mortality worldwide, representing 32% of all global deaths (World Health Organization, 2021) and 45% of NCD-related mortality (Roth et al., 2017). The reported association with periodontitis was explored in a joint Focused Workshop of the EFP and the World Heart Federation (WHF) in 2019 (Sanz, Del Castillo, et al., 2020; Sanz, Marco Del Castillo, et al., 2020).

Respiratory diseases, including chronic conditions (chronic obstructive pulmonary disease [COPD], asthma, obstructive sleep apnea [OSA]) and acute conditions (community-acquired pneumonia [CAP], COVID-19), are highly prevalent diseases. In 2019, lower respiratory tract infections and COPD were among the top 10 diseases inducing long-term disabilities (GBD 2019 Diseases and Injuries Collaborators, 2020), thereby significantly impacting public health. Indeed, 251 million patients worldwide were diagnosed with COPD in 2016 and it is expected to become the third highest cause of mortality by 2030 (GBD 2015 Chronic Respiratory Disease Collaborators, 2017).

In the previous EFP Focused Workshops on the association between periodontitis and diabetes (2017) and CVDs (2019), the crucial role of family doctors in the implications of these associations was clearly established. Therefore, a third Focused Workshop was designed together with the European arm of the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA Europe), aimed at exploring (1) the implications for dentists and family doctors of the associations between periodontal and systemic diseases and (2) the role of oral health professionals (OHPs) collaborating with family doctors in managing NCDs and promoting healthy life styles.

The specific aims of the Workshop were divided in two categories:

- Instrumental aims
  - To define the potential role of family doctors in the early detection/screening/prevention of periodontal diseases, including recommendations, questionnaires, self-reporting tools or other approaches;
  - To define the potential role of dentists/periodontists/oral health teams in the early detection/screening/prevention of NCDs, including CVDs, diabetes and respiratory diseases.
- Educational aims
  - To develop adequate information about periodontal diseases for family doctors;
  - To develop adequate information about NCDs (CVDs, diabetes and respiratory diseases) for dentists/periodontists/oral health teams;
  - To provide a biological rationale for the relevant associations between different NCDs, highlighting the importance of risk factors control (common risk factors approach) and healthy lifestyles.

This consensus report presents the conclusions of a Focused Workshop between the EFP and WONCA Europe, held in Madrid (Spain), in July 2022. During the Workshop discussions, the term "family doctors" was selected, although it is understood that "general practitioners/family physicians" is the official term. Therefore, in the present consensus report, the term "family doctors" is most often used.

2 | CARDIOVASCULAR DISEASES AND PERIODONTITIS

2.1 | Background

2.1.1 | Cardiovascular diseases and periodontitis

CVDs represent a large group of pathological conditions, which include ischemic heart disease, stroke, hypertension (leading to heart failure), rheumatic heart disease, cardio-myopathies and atrial fibrillation.

Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of the tooth-supporting apparatus.

There is evidence from epidemiological studies that periodontitis patients exhibit significant sub-clinical atherosclerosis. Similarly, there

is robust evidence for a positive association between periodontitis and coronary heart disease and stroke (Dietrich et al., 2013).

2.1.2 | Consequences of CVDs and periodontitis

CVDs are the leading cause of mortality worldwide, representing 32% of all global deaths (World Health Organization, 2021) and 45% of NCD-induced mortality (Roth et al., 2017), being responsible for 17.9 million deaths annually. Periodontitis, irrespective of severity, affects nearly half of the world adult population (Eke et al., 2018; Eke et al., 2020), while the most severe forms affect between 7.8% and 11% of all adults, representing in 2017 about 743 million people (GBD DALYs and Hale Collaborators, 2018; Kassebaum et al., 2014; Kassebaum et al., 2017). In 2019, 1.1 billion cases of severe periodontitis were present globally (Chen et al., 2021). Severe periodontitis, alongside with dental caries, is responsible for more years lost to disability than any other medical condition (GBD DALYs and Hale Collaborators, 2018) and it is a significant cause of tooth loss, nutritional compromise, altered speech, low self-esteem and poorer overall quality of life (Buset et al., 2016; Tonetti et al., 2017). Periodontitis has also been independently associated with premature death (Garcia et al., 1998; Linden et al., 2012; Sharma et al., 2016; Soder et al., 2007).

2.1.3 | Mechanisms underpinning the association between CVDs and periodontitis

Periodontitis is a chronic inflammatory disease initiated by the accumulation of a pathogenic dental plaque biofilm above and below the gingival margin. The initial inflammatory response drives microbial dysbiosis, which in turn leads to a chronic, non-resolving and destructive immune–inflammatory response characteristic of periodontitis (Meyle & Chapple, 2015; Tonetti et al., 2017). The mechanisms underpinning the association between periodontitis and CVDs have been explained by the passage of periodontal bacteria into the vascular system (bacteraemia), and by the increased levels of systemic inflammation resulting from periodontitis (Herrera et al., 2020; Reyes et al., 2013; Schenkein & Loos, 2013). Subjects with periodontitis experience frequent episodes of bacteraemia, particularly following daily life activities (tooth brushing, flossing and chewing) and professional interventions (dental prophylaxis, scaling, tooth extraction, surgical extraction of third molars and periodontal probing) (Reyes et al., 2013). DNAs from periodontal pathogens and viable bacteria have been identified in atherothrombotic tissues (Herrera et al., 2020; Rafferty et al., 2011; Reyes et al., 2013). These bacteria and/or their products and virulence factors may therefore influence the pathophysiology of atherosclerosis, as demonstrated in experimental pre-clinical models (Schenkein et al., 2020).

There is evidence indicating that periodontitis patients exhibit the following:

- Increased production and levels of inflammatory mediators associated with the pathophysiology of atherosclerosis, such as high-sensitivity C-reactive protein (CRP), and elevations in prothrombotic factors, which are also associated with the pathophysiology of atherothrombosis, such as fibrinogen, are also reported in periodontitis patients (Chandy et al., 2017);
- Elevated serum antibody levels that cross-react with antigens in cardiovascular tissues (Schenkein & Loos, 2013);
- Higher levels of dyslipidaemia including serum total cholesterol levels, low-density lipoproteins (LDLs), triglycerides, very low density lipoproteins (VLDL), oxidized LDL and phospholipase-A2 and lower high-density lipoprotein (HDL) levels (Teeuw et al., 2014);
- Peripheral blood neutrophils (PBNs), producing higher levels of total and extracellular reactive oxygen species (ROS), in comparison to periodontally healthy controls (Matthews et al., 2007).

Finally, periodontitis and CVDs share numerous common genetic (Aarabi et al., 2017; Loos & Van Dyke, 2020; Munz et al., 2018; Schaefer et al., 2015) and environmental risk factors (e.g., tobacco smoking) (Seitz et al., 2019).

2.1.4 | Outcomes from the 2019 EFP–WHF consensus workshop

This consensus Workshop focused on the epidemiological evidence of the association between CVDs and periodontitis, the mechanisms behind these associations and their consequences, derived from available intervention studies (Sanz, Del Castillo, et al., 2020; Sanz, Marco Del Castillo, et al., 2020).

Epidemiology

There is evidence from epidemiological studies for a positive association between periodontitis and coronary heart disease. Several systematic reviews conducted in the last 10 years have demonstrated a higher prevalence of coronary artery disease and risk of myocardial infarction and other coronary events in patients with clinically diagnosed periodontitis or more severe periodontitis. Similarly, there is epidemiological evidence for a positive association between periodontitis and cerebrovascular disease (Dietrich et al., 2013). An analysis of data from the ARIC study demonstrated an association between periodontal profile class and incident ischemic stroke; patients with periodontitis had more than double the risk of cardioembolic and thrombotic stroke compared to periodontally healthy individuals (Sen et al., 2018). In addition, there is an association between periodontitis and higher mortality rates, due to coronary heart disease and cerebrovascular disease (Dietrich et al., 2013).

This epidemiological evidence has been corroborated by observational cross-sectional data, from large population registry-based studies in South Korea (Park et al., 2019), Taiwan (Chou et al., 2015) and Sweden (Gustafsson et al., 2020), reporting that periodontitis is significantly associated with increased risk of a first cardiovascular event, heart failure and a higher incidence of atrial fibrillation. There is, however, limited but consistent evidence that individuals with periodontitis have a higher prevalence and incidence of peripheral artery disease

(PAD) and other CVDs or conditions, such as heart failure or atrial fibrillation (Yang et al., 2018).

There is also evidence from epidemiological studies that people with periodontitis have a higher prevalence of subclinical CVD, characterized by significant endothelial dysfunction (measured by flow-mediated dilation [FMD]), arterial stiffness (e.g., pulse wave velocity [PWV]), a significantly greater carotid intima media thickness (cIMT) and elevated arterial calcification scores. Furthermore, recent evidence also suggests that poor periodontal health is associated with an increased prevalence of hypertension (Del Pinto et al., 2020; Del Pinto et al., 2021; Munoz Aguilera et al., 2020).

Intervention studies

Despite the absence of prospective randomized clinical trials (RCTs) demonstrating that periodontal therapeutic interventions significantly reduce cardiovascular events, observational evidence suggests that different oral health interventions, including self-performed oral hygiene habits (toothbrushing), dental prophylaxis (professional mechanical plaque removal), increased self-reported dental visits and periodontal treatment, resulted in a reduction in the incidence of CVD events (de Oliveira et al., 2010). There is moderate evidence that periodontal treatment results in the reduction of low-grade inflammation as assessed by serum levels of CRP, interleukin (IL)-6 and improvements in surrogate measures of endothelial function (FMD of the brachial artery) (Ling et al., 2016; Orlandi et al., 2020). Similarly, there is still limited available evidence for the effect of periodontal therapy on reducing arterial hypertension (Orlandi et al., 2022).

2.2 | Objectives of WONCA Europe–EFP Workshop on the association between CVDs and periodontitis

The objective of the present WONCA Europe–EFP Workshop was to summarize the evidence on the association between periodontitis and CVDs accumulated in the last 5 years and to provide recommendations for family doctors and dental practitioners. Therefore, this consensus report is based on the 2019 Workshop consensus publications (Sanz, Marco Del Castillo, et al., 2020; Sanz, Del Castillo, et al., 2020), the supporting narrative reviews (Herrera et al., 2020; Orlandi et al., 2020; Schenkein et al., 2020), the EFP S3 level clinical practice guidelines (Herrera et al., 2022; Sanz, Herrera, et al., 2020) and a systematic review purposely written for the most recent guideline (Orlandi et al., 2022).

2.3 | Summary of evidence and guidance

2.3.1 | Should oral healthcare professionals participate in screening for CVD risk in patients in the dental practice?

OHPs should advise patients with periodontitis that their risk for CVDs, such as myocardial infarction or stroke, is higher. They should collect a careful history to assess for CVD risk factors, such as diabetes, obesity, smoking, hypertension, hyperlipidaemia and hyperglycaemia. Furthermore, they should actively screen for cardiovascular risk factors (physical activity, excess weight, blood pressure, lipid and glucose management) and advise their patients on adequate preventive measures.

When patients present with obvious risk factors, they should be advised to consult their family physician and to promote active lifestyle measures to reduce CVD risk, such as increased physical activity, weight loss, smoking cessation and so on.

In patients with periodontitis and a diagnosis of CVD, OHPs should advise them that they may be at higher risk for subsequent CVD complications, and therefore they should not only adhere to the recommended periodontal preventive measures and regular supportive periodontal treatment but also adopt adequate preventive measures to reduce/control cardiovascular risk factors.

2.3.2 | Can treatment of periodontitis reduce the risk of adverse CVD events?

There are currently no prospective randomized controlled periodontal intervention studies on primary prevention of CVDs (including first ischemic events or cardiovascular death). However, consistent observational evidence suggests that oral health interventions and periodontal treatment can lead to a reduction in the incidence of acute cardiovascular disease (ACVD) events and that the progression of ACVD can be influenced by successful periodontal treatment, independently of traditional CVD risk factor management.

Although there is one pilot multi-centre study on secondary prevention of ACVD events, reporting no statistically significant differences in the rate of CVD events between patients who underwent treatment of periodontitis versus community care, these data are of limited applicability/usefulness due to significant methodological limitations of the study. Therefore, there is insufficient evidence to support or refute the potential benefit of the treatment of periodontitis in preventing or delaying secondary ACVD events.

2.3.3 | Can treatment of periodontitis reduce CVD risk as measured through surrogate markers?

There is clear evidence on the effect of periodontal therapy on surrogate markers of CVD. There is a significant effect of periodontal treatment in reducing low-grade inflammation as assessed by serum levels of CRP, IL-6 and improvements in surrogate measures of endothelial function (FMD of the brachial artery). There is also evidence that periodontal treatment reduces arterial blood pressure and stiffness and sub-clinical ACVD marker (as assessed by mean cIMT).

Periodontal treatment, however, has not demonstrated any significant effect on lipid fractions or on ACVD biomarkers of coagulation, endothelial cell activation or oxidative stress.

2.3.4 | Can treatment of periodontitis increase the risk of CVD events?

Delivering periodontal treatment is safe regarding cardiovascular risk (in patients with established CVD). In people who have experienced a recent acute CVD event, if periodontitis is diagnosed, treatment should start as soon as their cardiovascular status permits, and a consultation with the treating family doctor/cardiologist is advised.

Irrespective of the severity of CVD or specific medication, non-surgical (steps 1 and 2) periodontal therapy should be provided, preferably in several 30–45-min sessions to minimize the spike of acute systemic inflammation, documented to arise as a result of the treatment-generated bacteraemia.

Surgical periodontal and implant therapy, when indicated, should be provided in a similar manner as for patients without CVD. However, attention should be paid to the following:

- Hypertension. It is recommended to measure the patient's blood pressure (after appropriate relaxation) before surgical intervention, and in cases of high blood pressure (above 180/100 according to expert opinion), the surgery should be postponed until the patient's blood pressure has been stabilized.
- Treatment with anti-platelet and anti-coagulant drugs. Because periodontal and implant surgical procedures usually impart only a low to medium risk of bleeding in general terms, the dentist should not change a patient's medications, or in cases of doubt, he/she should consult the family physician/cardiologist prior to the surgical intervention. Consideration should also be given to the local management of bleeding complications that may arise.

2.3.5 | Is treatment of periodontitis safe in patients with CVDs?

Periodontal treatment in CVD patients is safe, although in some cases (e.g., where patients receive anti-coagulant or anti-platelet therapy) safe and careful haemostatic measures need to be taken.

In people who have experienced a recent acute CVD event, if periodontitis is diagnosed, treatment should start as soon as their cardiovascular status permits, and a consultation with the treating family doctor/cardiologist is advised.

The recommendations for non-surgical (steps 1 and 2) periodontal therapy, for surgical periodontal therapy (step 3) and for surgical implant therapy should follow those already described in Section 2.3.4.

2.3.6 | Should family physicians screen for periodontal health in CVD patients?

Family physicians should ask patients with CVD about signs and symptoms of periodontitis (such as bleeding gums and loose teeth) and, where appropriate, recommend a periodontal evaluation.

2.3.7 | Guidance for healthcare funders

The recommendations above assume that access to universal health care includes access to an oral health assessment and treatment, although it is understood that such access may not be universal across Europe. The recent World Health Organization Resolution (WHO, 2021) urges Member States to address key risk factors for oral diseases that are shared with other NCDs and to enhance the scope of practice of OHPs. It also recommends that oral health should be firmly embedded within the NCD agenda and that oral healthcare interventions should be included in universal health coverage programmes.

3 | DIABETES AND PERIODONTITIS

3.1 | Background

3.1.1 | Prevalence of type 2 diabetes and periodontitis

Diabetes and periodontitis are highly prevalent NCDs that are bidirectionally related epidemiologically (Sanz et al., 2018a), biologically (Chapple, Genco, & Working group 2 of joint, 2013) and therapeutically (Graziani et al., 2018), and with co-morbid consequences (Sanz et al., 2018a). The global prevalence of diabetes in 2019 was estimated at 9.3% (463 million people) and is expected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi et al., 2019). The global prevalence of severe periodontitis was estimated in 2017 as 743 million (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018) and 1.1 billion in 2019 (Chen et al., 2021), amounting to between 7.8% and 11% of adults (Kassebaum et al., 2014; Kassebaum et al., 2017).

3.1.2 | Consequences of type 2 diabetes and periodontitis

Type 2 diabetes is a major cause of disability and premature mortality, mainly from vascular and renal complications (Tuomi et al., 2014). There are currently 22 million people living with undiagnosed diabetes in Europe (International Diabetes Federation, 2021), many of whom attend a dental surgeon 6-monthly but do not necessarily engage regularly with their family doctor (Yonel et al., 2018). In contrast, there are several countries in Europe where patients visit their family doctor several times a year (Björnberg & Phang, 2018) but may not necessarily engage frequently with their family dentist. Periodontitis, alongside dental caries, is responsible for more years lost to disability than any other human condition (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018) and is a significant cause of tooth loss, nutritional compromise, altered speech, low self-esteem and poorer overall quality of life (Al-Harthi et al., 2013; Buset et al., 2016) and is independently associated with premature mortality (Garcia

et al., 1998; Linden et al., 2012; Sharma et al., 2016; Soder et al., 2007).

3.1.3 | Mechanisms underpinning bidirectional relationship between type 2 diabetes and periodontitis

As explained in the introduction, periodontitis is a chronic inflammatory disease initiated by the accumulation of a pathogenic dental plaque biofilm above and below the gingival (gum) margin, and within which microbial dysbiosis leads to a chronic, non-resolving and destructive inflammatory response (Meyle & Chapple, 2015; Tonetti et al., 2017). Mechanisms of association between periodontitis and type 2 diabetes include periodontal bacteraemia during daily function (Reyes et al., 2013), where a dose–response relationship has been demonstrated in vascular inflammation (Desvarieux et al., 2005), systemic oxidative stress negatively impacting β-cell function (Allen et al., 2011) and systemic inflammation expressed through pro-inflammatory signatures in serum (Polak & Shapira, 2018). The mechanisms driving adverse periodontal outcomes arising in diabetes patients with hyperglycaemia are believed to include exaggerated systemic inflammation due to the impact of glucose levels (Esposito et al., 2008), frequency of glucose intake on systemic inflammation (Ceriello et al., 2008), negative impacts upon neutrophil functional efficiency (Engebretson et al., 2006), T-helper-1, -2 and -17 cell responses (Duarte et al., 2011) and advanced glycation end-product formation, inhibiting periodontal wound healing (Taylor et al., 2013).

3.1.4 | Outcomes from 2017 EFP–IDF consensus Workshop

The significant and independent association between periodontitis and diabetes is widely reported in the literature. Such an evidence base provided the impetus for an EFP–IDF Focused Workshop in 2017, where consensus statements were developed (Sanz et al., 2018a, 2018b) based upon three systematic reviews addressing epidemiology (Graziani et al., 2018), biological mechanisms (Polak & Shapira, 2018) and periodontal intervention studies (Madianos & Koromantzos, 2018). The main conclusions of the 2017 Focused Workshop were as follows:

In the diabetes–periodontitis direction, poorly controlled type-1 and type-2 diabetes are associated with an increased risk and severity of periodontitis, whereas well-controlled diabetes patients exhibit no increased risk of progressive attachment loss relative to people without diabetes (Demmer et al., 2012). Clinical periodontal parameters and local inflammatory biomarkers improve following standard and successful non-surgical periodontal therapy, even in people with poor diabetes control (Sanz et al., 2018a). Also, systemic inflammatory biomarkers improve after non-surgical periodontal therapy in people with diabetes, and improvements are greater in individuals with diabetes and periodontitis compared to those with periodontitis without diabetes (Preshaw et al., 2020).

In the periodontitis–diabetes direction, severe periodontitis was associated with significantly elevated serum levels of HbA1C in people without diabetes (glycaemia) and in those with diabetes (hyperglycaemia) (Graziani et al., 2018). There appeared to be a direct relationship between the severity of the periodontitis and complications of diabetes. The evidence also indicates that people with severe periodontitis have an increased risk of developing type 2 diabetes (Graziani et al., 2018). Finally, in the systematic review aimed at addressing the impact of periodontal treatment on plasma HbA1C levels, a mean reduction in HbA1C of 0.36% (95% CI: 0.19–0.54) was demonstrated at 3 months (Engebretson & Kocher, 2013), a result that was consistent with previous meta-analyses. Data from four systematic reviews with meta-analyses have provided consistent evidence that successful periodontal therapy results in a clinically meaningful and statistically significant reduction of HbA1C levels in people with type 2 diabetes, ranging from 0.27% to 0.48% at 3–4 months following periodontal therapy (Madianos & Koromantzos, 2018). A 12-month randomized controlled trial, where intensive periodontal treatment was undertaken to achieve a healthy periodontal endpoint, demonstrated 0.6% reductions in HbA1C (D'Aiuto et al., 2018).

3.2 | Objectives of WONCA Europe–EFP Workshop on the association between diabetes and periodontitis

The objective of Working Group 2 of the present WONCA Europe–EFP Workshop was to summarize the evidence base on the bidirectional association between periodontitis and diabetes and provide recommendations for family medical and dental practitioners. As explained before, the bases for the discussion were the conclusions of the EFP–IDF Focused Workshop in 2017 (Sanz et al., 2018a, 2018b), the three systematic reviews prepared for that Workshop, addressing epidemiology (Graziani et al., 2018), biological mechanisms (Polak & Shapira, 2018) and periodontal intervention studies (Madianos & Koromantzos, 2018), newly published reviews (Genco et al., 2020; Genco & Borgnakke, 2020; Genco & Sanz, 2020; Jepsen et al., 2020; Polak et al., 2020) and studies, the EFP S3 level clinical practice guidelines (Herrera et al., 2022; Sanz, Herrera, et al., 2020) and a systematic review on the impact of periodontitis treatment on systemic outcomes (Orlandi et al., 2022).

3.3 | Summary of evidence for the association between diabetes and periodontitis

3.3.1 | Periodontitis–diabetes direction

Do people with periodontitis have a greater risk of developing type 2 diabetes?

Overall, evidence from six studies representing populations from the United States, Japan and Taiwan, with a total sample of 77,716

participants, consistently demonstrated that patients with periodontitis exhibit a higher chance of developing pre-diabetes, referred to as non-diabetic hyperglycaemia (NDH) and diabetes (adjusted hazard ratio [HR] range: 1.19–1.33). Given the high prevalence of periodontitis in the population and the fact that periodontitis can be easily diagnosed and treated, even small adjusted HRs have potentially important public health implications (Sanz et al., 2018a).

A recent large-scale study was carried out in Korea, using data from adult volunteers without diabetes who received health screening (National Health Insurance Service-National Health Screening cohort database, $n = 111{,}611$) (Park, Kim, et al., 2022). During a median follow-up of 9.1 years, diabetes developed in 6102 volunteers. It was reported that people who recovered from periodontitis had a lower risk of developing diabetes than those who had unresolved chronic periodontitis (adjusted HR = 0.930, 95% CI: 0.865–1.000, $p = .050$), whereas those who developed periodontitis had a higher risk for diabetes in a multivariate regression model than those who remained periodontally healthy (adjusted HR = 1.095, 95% CI: 1.026–1.170, $p = .006$) (Park, Kim, et al., 2022). This new data adds to the existing evidence base (Sanz et al., 2018a) that periodontitis appears to be a component cause of type 2 diabetes in some patients.

Do people with periodontitis and diabetes experience greater complications related to diabetes?

Complications of diabetes studied in relation to periodontitis are retinopathy (background and proliferative), nephropathy (macroalbuminuria and end-stage renal disease), neuropathic foot ulceration, various CVDs and mortality (Sanz et al., 2018a).

A recent systematic review analysed the available evidence (Nguyen et al., 2020). The overall synthesis is drawn from a total of 8969 patients with diabetes in 13 studies, ranging from 73 to 6048 participants (type 1, $n = 3591$; type 2, $n = 5378$). For people with diabetes and periodontitis, higher risks were reported for retinopathy (odds ratio [OR] range = 2.8–8.7), neuropathy (OR range = 3.2–6.6), nephropathy (OR range = 1.9–8.5), cardiovascular complications (OR range = 1.28–17.7) and mortality (OR range = 2.3–8.5), compared to those with diabetes and no periodontitis.

A systematic review (Graziani et al., 2018), prepared for the EFP–IDF Focused Workshop in 2017 (Sanz et al., 2018a), indicated that the severity of periodontitis correlates significantly with the severity of retinopathy and that people with periodontitis, with either type 1 or type 2 diabetes, have significantly more renal complications.

In one large study (13,784 subjects), chronic kidney disease (CKD) was associated with significantly greater all-cause and cardiovascular mortality when periodontitis and diabetes were present at the same time as CKD than when either was present as an individual and independent comorbidity with CKD (Sharma et al., 2016). In another recent large-scale study in the Republic of Korea (11,353 diabetes participants) (Park, Jeon, et al., 2022), multivariable regression analyses revealed that periodontitis is an independent risk factor for diabetes-related microvascular complications (adjusted HR = 1.13, 95% CI: 1.04–1.23, $p = .004$). In the secondary analysis for individual microvascular complications, periodontitis was an independent risk factor for retinopathy (adjusted HR = 1.21, 95% CI: 1.04–1.40, $p = .013$).

In summary, the majority of studies report a higher association/risk between poorer periodontal health and diabetes complications.

Should OHPs assess patients in the dental practice/office for diabetes risk?

There are an estimated 22 million people in Europe with undiagnosed diabetes mellitus (International Diabetes Federation, 2021). Evidence from a UK study showed that 12% of the public who attended a dentist regularly had not seen their family doctor in 12 months and that, of 61% of the public who attend a dental office biannually, 48% had never had a healthcare check-up with their family doctor. Therefore, OHPs have access to a section of society that may not engage with their family doctor and may not have undergone a recent healthcare check-up, but who do attend their dental practice regularly for oral health assessments and comply with both primary and secondary prevention of oral diseases (Yonel et al., 2018). Given the high prevalence of periodontitis in the population, the three-fold increased prevalence of periodontitis in patients with type 2 diabetes (Tsai et al., 2002), the increased risk of incident diabetes in periodontitis patients (Chapple et al., 2013; Sanz et al., 2018a), the higher complication rates of diabetes in periodontitis (Borgnakke et al., 2013) and the obligation for dental teams to screen for periodontitis, OHPs are ideally placed to help identify people at high risk of pre-diabetes/NDH or type 2 diabetes.

There is broad stakeholder support for risk-targeted early case detection of pre-diabetes/NDH and diabetes in dental as well as pharmacy settings, a consistent finding reported in several countries across the world. Patients (Creanor et al., 2014; Greenblatt et al., 2017; Yonel et al., 2018), members of the public (Yonel, Batt, et al., 2020), family doctors (Greenberg et al., 2015; Yonel et al., 2018), dental surgeons (Esmeili et al., 2010; Yonel, Batt, et al., 2020) and dental hygienists (Greenberg et al., 2017), all broadly support greater involvement of OHPs in early case identification of dysglycaemia. In the United Kingdom, the National Institute for Health and Care Excellence (NICE), which provides guidance and advice for health and social care in England, but also some services for Scotland, Wales and Northern Ireland, recommends that dental teams should identify those at high risk of diabetes type 2 using a validated tool (National Institute for Health and Care Excellence, 2017). Such tools have been established and evaluated in several countries such as the United States (Borrell et al., 2007), Spain (Montero et al., 2021) and the United Kingdom (National Institute for Health and Care Excellence, 2015a, 2015b; Yonel, Yahyouche, et al., 2020) and shown to have some utility as a single-step protocol. However, emerging evidence shows that the addition of periodontal measures may further improve the performance of such risk prediction questionnaires (Talakey et al., 2021).

There is a clear need for oral healthcare teams to be educated on the impact of periodontitis on diabetes risk and made aware of the most effective protocols for diabetes risk assessment (National

Institute for Health and Care Excellence, 2017). Formal training of OHPs has been shown to be an important factor in the behavioural patterns of dentists towards diabetes (Esmeili et al., 2010).

What is the optimal pathway for early case detection of diabetes in dental practice?

Screening, risk assessment and early case detection of type 2 diabetes and pre-diabetes/NDH have been shown to be feasible in dental office settings (Borrell et al., 2007; Genco et al., 2014; Lalla et al., 2011; Montero et al., 2021). In a US-based study, self-reported family history of diabetes, hypertension, hypercholesterolaemia and clinical evidence of periodontitis gave a probability of undiagnosed diabetes of 27%–53% (Borrell et al., 2007). A model that included only two dental variables (percentage of deep pockets ≥5 mm and the number of missing teeth) provided an area under the receiver operator curve (AUROC) of 0.65, with the addition of a point-of-care (POC) HbA1C test improving the AUROC to 0.79. Optimal cut-off points were determined as the presence of ≥26% deep pockets or ≥4 missing teeth, and these correctly identified 73% of true cases of pre-diabetes/NDH or diabetes, and the inclusion of a POC HbA1C test value of ≥5.7% further improved correct identification (Lalla et al., 2011). Recently, a risk prediction questionnaire developed specifically for dental offices, employing a large sample size (>4000) and validated internally and externally in a German population with 357 events, produced an AUROC of 0.7 and positive predictive value of 91.5% (95% CI: 91.5–91.6) (Yonel et al., 2022).

The term "screening" is becoming problematic in the context of detection of diabetes, as it traditionally implies an untargeted approach to a population-level testing (such as assessing all people over the age of 40 years). This is unlikely to be cost effective or efficient, and the use of questionnaires to determine risk status provides a more targeted and efficient approach. However, such questionnaires should be internally and externally validated within the population that they are to be employed within, and should be based upon large sample sizes to validate multivariable prediction models, and with a sufficient number of "events" arising within that sample (Collins et al., 2016; Riley et al., 2019; Riley et al., 2020). It has been suggested that a minimum of 100 events, and ideally more than 250 events, are required to validate such models (Steyerberg, 2019). Currently, models developed and reported for use in dental care settings have not justified sample sizes and have reported relatively small sample sizes with few "events" (Heji et al., 2021; Su et al., 2020).

In some studies, to overcome the challenges of risk assessment questionnaires for use in dental settings, a two-step protocol has been employed. The risk questionnaire represents the first step, and when the threshold designating "high risk" is exceeded, a blood test is carried out to determine HbA1C status. This protocol has been employed in several studies to date and could potentially reduce unnecessary referrals to family doctors for formal diagnosis by 90% (Yonel, Yahyouche, et al., 2020).

Bould et al. (Bould et al., 2017) showed that the use of a two-step risk assessment model using the Finnish Diabetes Risk Score (FINDRISC) followed by capillary blood (finger prick) HbA1C testing was psychologically acceptable and helped patients to engage with contacting their family doctor, the OR being 3.22 times higher than for the questionnaire alone. An RCT of undiagnosed patients (Lalla et al., 2015) found that informing patients about their diabetes risk and sharing their venous blood HbA1C test result in a dental office setting led to 86% visiting their family doctor within 6 months, at least one positive lifestyle change being made and a decrease of 1.46 ± 0.28% in HbA1C compared to baseline ($p < .01$).

Increased co-operation between OHPs and family doctors is essential for successful diagnosis of diabetes following risk assessment in dental settings (Engstrom et al., 2013; Lalla et al., 2015). Such collaborative working was recommended in a white paper by the Economist Intelligence Unit (Economist Intelligence Unit, 2021) and also in an NHS England commissioning standard (National Health Service, 2019).

Can treatment of periodontitis reduce HbA1C levels and complications in diabetes patients?

A recent Cochrane review (Simpson et al., 2022) analysed the available evidence on the impact of periodontal treatment on diabetes outcomes and updated the Cochrane reviews published in 2010 and 2015. It evaluated periodontal treatment versus no periodontal intervention or "usual care". The update included 35 studies (reported in 53 publications) involving a total of 3249 randomized participants for a narrative synthesis; 33 of the studies (reported in 51 publications) were included in a meta-analysis. All studies were parallel RCTs. Thirty-four of 35 studies analysed type 2 diabetes, while one study addressed both type 1 and type 2 diabetes. Twenty-one studies assessed the effects of subgingival instrumentation versus no treatment/usual care, 11 studies assessed subgingival instrumentation plus systemic or locally delivered anti-microbial drugs versus no treatment/usual care and 3 studies assessed subgingival instrumentation plus an anti-microbial mouth rinse (chlorhexidine) versus no treatment/usual care. Most of the studies (30, $n = 2443$ subjects) measured the outcomes at 3–4 months, and 12 studies ($n = 1457$) reported data at 6 months. Only one study reported outcomes at 12 months ($n = 267$) (D'Aiuto et al., 2018). The data provided evidence that periodontal therapy resulted in clinically meaningful and statistically significant reductions of HbA1C levels in people with type 2 diabetes. The magnitude of reported HbA1C reductions from these meta-analyses was 0.43% (95% CI: 0.28%–0.59%) at 3–4 months following periodontal therapy, 0.3% at 6 months (95% CI: 0.08%–0.52%) and 0.5% at 12 months (95% CI: 0.45%–0.55%). These results are consistent with a previous report (Madianos & Koromantzos, 2018; Sanz et al., 2018a). This 2022 update of the former Cochrane reviews included double the number of studies and participants and led to a change in the conclusions related to the primary outcome measure of glycaemic control and in the level of certainty of the conclusion. There is now a moderate level of certainty that periodontal treatment using subgingival instrumentation improves glycaemic control in people with both periodontitis and diabetes by a clinically significant amount compared to no treatment or usual care.

There is insufficient evidence concerning the effect of periodontal therapy on HbA1C reduction in patients with type 1 diabetes due to a lack of studies. However, the biological plausibility linking periodontal therapy to improved glycaemic control may also apply to people with type 1 diabetes mellitus. This is recognized in the 2022 NICE guidelines on diagnosis and management of type 1 and type 2 diabetes in adults (National Institute for Health and Care Excellence, 2022).

The magnitude of short-term HbA1C reductions obtained following periodontal interventions is similar to that achieved by adding a second medication to a metformin pharmacological regime (Engebretson & Kocher, 2013). If such reductions following periodontal therapy can be sustained and over a long term, this may contribute to reduced diabetes-associated morbidity and mortality and also reduce pharmacological costs.

3.3.2 | Diabetes–periodontitis direction

Can diabetes control affect the progression of periodontitis and peri-implantitis?

A large longitudinal population-based study was conducted in Germany over 5 years and found that individuals with uncontrolled type 2 diabetes had greater progression of periodontitis than those with controlled or no diabetes. In addition, the study reported that greater tooth loss arose in uncontrolled type 1 and type 2 diabetes compared with groups with controlled or no diabetes (Demmer et al., 2012; Genco & Borgnakke, 2020).

The possible association between diabetes and peri-implantitis was the subject of a meta-analysis (seven studies), which detected the risk of peri-implantitis as approximately 50% higher in people with diabetes than in those without diabetes (RR = 1.46, 95% CI: 1.21–1.77, and OR = 1.89, 95% CI: 1.31–2.46; $z = 5.98$, $p < .001$). Importantly, among non-smokers, those with hyperglycaemia had a 3.39-fold higher risk for peri-implantitis compared to those with normoglycaemia (95% CI: 1.06–10.81) (Monje et al., 2017).

Can diabetes control affect the response to periodontal treatment?

A longitudinal study followed patients for 5 years post periodontal treatment during supportive periodontal care. The progression of periodontitis was significantly greater among patients with diabetes and poor glycaemic control (mean HbA1C = 9.1%) than those with diabetes and good glycaemic control (mean HbA1C = 6.1%) and in people without diabetes. Moreover, tooth loss was greater over the 5 years in those with diabetes and poor glycaemic control compared with those with good glycaemic control or no diabetes (Costa et al., 2013; Genco & Borgnakke, 2020).

Should family doctors refer patients with pre-diabetes/NDH or type-2 diabetes for a comprehensive oral health assessment?

Periodontitis is highly prevalent in the population world-wide with prevalence estimates consistently reported as 45%–50% for most nations and severe disease impacting 7.8%–11.2% of the world population (Kassebaum et al., 2014; Kassebaum et al., 2017). Periodontal diagnosis currently requires a clinical examination by a suitably trained OHP. However, a significant proportion of the population does not routinely attend dental practices/offices for such examinations, although they visit their family doctor at least annually (Yonel et al., 2018).

Montero and colleagues (Montero et al., 2019) developed an internally validated predictive model for moderate to severe periodontitis using the 2011–2012 National Health and Nutrition Examination Survey (NHANES) data from the United States and the CDC/AAP classification for moderate and severe periodontitis (total percent affected 50.3). In a multivariate logistic regression model for an HbA1C cut-off of ≥5.7%, they showed that individuals with an HbA1C above this threshold had 29% increased odds of having periodontitis ($p < .01$). A predictive model that included age, gender, ethnicity, smoking and HbA1C produced a sensitivity of 70% and a specificity of 67.7%. This model, however, is only relevant to a US population and would need validation in relevant European populations for its use in those countries.

An alternative approach to permit early case detection of periodontitis in non-dental settings is to develop lateral flow approaches for saliva biomarker panels that have been shown to discriminate between periodontal health, gingivitis and periodontitis. Grant et al. (Grant et al., 2022) reported that a panel of saliva biomarkers, which included matrix metalloproteinase (MMP)-9, alpha-1 acid glycoprotein, pyruvate kinase and S100A8, provided an AUROC of 0.96 (95% CI: 0.943–0.977) with a sensitivity of 97% and specificity of 82% for discriminating periodontal health or gingivitis from periodontitis. The adaptation of biomarker panels to lateral flow devices and their validation in specific populations may offer the opportunity for non-dental–care professionals to engage in early case detection for periodontitis in people with pre-diabetes/NDH or diabetes.

In light of the importance of periodontal diagnosis and treatment upon diabetes outcomes, and based on the recommendations from the 2017 EFP–IDF Workshop (Sanz et al., 2018a), NHS England (NHSE) developed a commissioning standard on dental care for people with diabetes. The standard was approved by the British Government and published in 2019 (National Health Service, 2019). Its purpose was "to ensure that people with diabetes can access effective oral healthcare services with the aim of improving their general and oral health". The commissioning standard aims to ensure that local care pathways and services are commissioned, based upon an oral health needs assessment for that region to determine whether existing oral care services are adequate for patients with diabetes. There is, therefore, now a requirement to implement the recommendations when periodontal services are commissioned in England. The diabetes pathway (Figure 1) outlines the journey that patients with type 1 or type 2 diabetes or those with pre-diabetes/NDH should embark upon.

There is an emerging trend for policy makers to recognize the importance of the periodontal–diabetes relationship, including the need for family doctors to assess the risk for periodontitis in their pre-diabetes/NDH or diabetes patients and to refer accordingly to the oral healthcare team for formal diagnosis and management as appropriate.

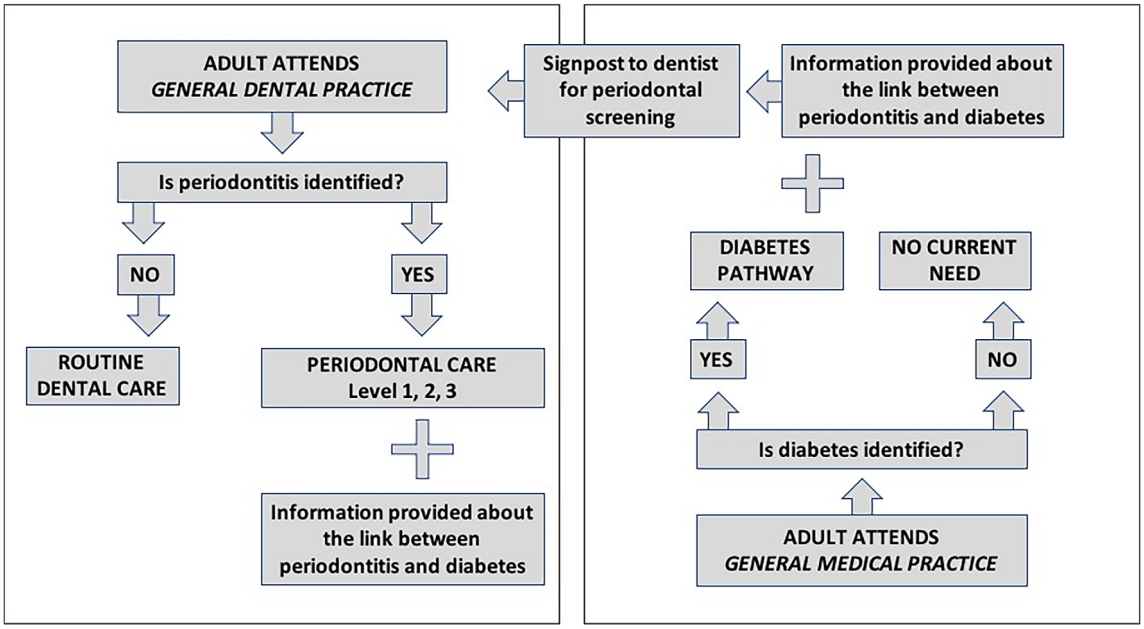

FIGURE 1 Flow-chart detailing clinical care pathway for patients diagnosed with diabetes (from general medical practitioner to general dental practitioner, and appropriate triage – Level 1, 2 or 3). Adapted from NHSE commissioning standard 2019 (National Health Service, 2019). Level 1 = general dental practitioner with no enhanced skills; Level 2 = enhanced skill practitioner but not at specialist level; Level 3 = specialist in periodontology.

What data is available on the return on financial investment of periodontal care for people with diabetes?

In 2021, the Economist Intelligence Unit (EIU) published a white paper on the health and economic costs of periodontitis (Economist Intelligence Unit, 2021). Their economic model was based upon six major European economies for which requisite data were available: Germany, France, Italy, Netherlands, Spain and the United Kingdom. The EIU analysed the costs and return on investment over a 10-year period of managing moderate periodontitis. The model calculated direct costs of care, as well as indirect costs (time off work) and intangible costs (healthy life years). The extreme scenario of 90% of cases of periodontitis being diagnosed and treated was the most expensive to deliver, but still provided a positive return on investment in all six nations. More importantly, neglecting to manage gingivitis and periodontitis increased costs and resulted in a reduction in healthy life years.

The EIU work was based upon periodontitis patients without co-morbidities such as diabetes. However, a recent NICE (2022) guideline in the United Kingdom analysed the cost effectiveness of treating periodontitis in people with diabetes (National Institute for Health and Care Excellence, 2022). Only one publication was found that was relevant to the population in question (Solowiej-Wedderburn et al., 2017), but NICE concluded that periodontal therapy may be cost effective for patients with type 2 diabetes provided the improvements in HbA1C could be maintained. An independent analysis in the same population was undertaken as part of an NHS England commissioning standard (National Health Service, 2019), which estimated the cost savings to the NHS of approximately £124 million per year from successful periodontal therapy. A US-based study (Jeffcoat et al., 2014) of insurance claims from 338,891 people showed significant reductions in medical care costs and hospital admissions (39.4%, $p < .05$) for those who received complete periodontal treatment; for people with diabetes, costs were 40.2% lower with an estimated annual medical care cost saving of $2840 per patient ($p < .04$). These results should be interpreted with caution because of the limitations inherent in the analysis (Sheiham, 2015).

Overall, there is a paucity of cost effectiveness data on periodontal treatment in diabetes patients, but the available data demonstrate significant economic benefit in the populations studied, provided periodontal outcomes and associated HbA1C reductions are maintained.

3.4 | Guidance: Diabetes–periodontitis

3.4.1 | General guidance

1. There is a need to raise awareness among family doctors, general dentists, other health professionals, patients and health authorities of the importance of periodontitis to diabetes control and complications and of the impact of hyperglycaemia upon periodontitis and compromised healing following periodontal therapy.
2. Bidirectional communication between family doctors and OHPs is key to collaborative management and should be documented in the patient's health record and ideally be supported by written communication between the two teams.

3.4.2 | Guidance for oral healthcare professionals

1. The OHP should inform patients with pre-diabetes (NDH)/diabetes about their increased risk of periodontitis and its impact on glycaemic control and its complications. They should then conduct a thorough periodontal examination, including a full periodontal chart and radiographs, and record signs of inflammation (bleeding on probing).

   i. For individuals with periodontal health, as defined in the 2018 classification (Caton et al., 2018), primary prevention measures for periodontitis should be undertaken (Chapple et al., 2015).
   ii. If gingivitis is diagnosed, it should be treated as a primary prevention strategy for periodontitis (Chapple et al., 2015). The need for optimal control of diabetes should also be emphasized, and regular visits to the family physician should be encouraged.
   iii. If periodontitis is diagnosed, the OHP should treat the patient according to the recent EFP treatment guidelines (Herrera et al., 2022; Sanz, Herrera, et al., 2020) and inform the family doctor of the diagnosis of periodontitis. If the patient does not have a family doctor, they should be advised to register with one.
   iv. People with diabetes should be informed of an increased risk for peri-implantitis.

2. Periodontal treatment in pre-diabetes/NDH and diabetes should ideally be performed to a defined endpoint of no periodontal pockets of >4 mm with bleeding on probing or deep pockets (≥6 mm) (Sanz, Herrera, et al., 2020), and if this endpoint is not achieved in general dental practice, such patients should be referred to a periodontal specialist. Stable patients should be enrolled in a regular supportive periodontal care programme, with a frequency of visits appropriate to their needs.
3. Undiagnosed pre-diabetes/NDH and diabetes may significantly impact an individual's health. The oral healthcare team should be aware that multiple periodontal abscesses in untreated patients, and/or a poor response to optimal periodontal treatment, can indicate an undiagnosed metabolic condition and such individuals' risk for diabetes should be assessed according to national guidelines for the management of such patients. Options for onward care include the following:

- Referral to a family doctor for further evaluation according to national guidelines;
- Undertaking risk assessment using a questionnaire validated for that population and onward referral to a family doctor for those with elevated risk (one-step protocol);
- Undertaking a two-step protocol whereby patients at high risk according to a validated questionnaire undertake a POC HbA1C test and further a referral if HbA1C values exceed cut-offs defined by national guidelines. This option is optimal but may not be feasible in all settings.

3.4.3 | Guidance for family doctors

People with diabetes are frequently unaware of their increased risk of developing periodontitis and its impact upon the control of diabetes, and they may not be engaged in regular professional oral care. We recommend the following:

1. For pre-diabetes (NDH)/diabetes patients who have not been examined for periodontitis or peri-implantitis, family doctors should discuss with them, as a routine part of their regular reviews

- that hyperglycaemia increases their risk of periodontitis and consequential tooth loss, as well as the effect that periodontitis may have on diabetes control and its complications;
- that periodontal treatment can improve their glycaemic control and may reduce future diabetes complications;
- the importance of regular oral health assessments and periodontal care tailored to individual needs;
- that emerging evidence demonstrates an increased risk for peri-implantitis in people with diabetes.

Family doctors should then refer patients with type 2 diabetes to the oral healthcare team for regular oral health assessments (National Institute for Health and Care Excellence, 2022).

2. For pre-diabetes (NDH)/diabetes patients who have been diagnosed with periodontitis, family doctors should

- advise them that improving glycaemic control improves periodontal treatment outcomes;
- encourage them to stick to regular oral healthcare appointments to manage their periodontitis (National Health Service, 2019; National Institute for Health and Care Excellence, 2022).

3.4.4 | Guidance for healthcare funders

In some European countries, people with diabetes are provided with free-of-charge fundoscopic assessment for diabetic retinopathy and podiatric services, to support their health and well-being and to reduce diabetic complications, yet periodontal care has to be paid for out of pocket by the patient. Given the health and economic benefits of successful periodontal treatment in patients with diabetes, it is time to address this historical anomaly. State-funded periodontal examinations, and treatment, if required, for patients with diabetes and pre-diabetes/NDH, appears justified on both health and economic grounds. Periodontal care for people with diabetes should be provided, in line with the current EFP S3-Level treatment guidelines for stage I-III and stage IV periodontitis (Herrera et al., 2022; Sanz, Herrera, et al., 2020).

4 | RESPIRATORY DISEASES AND PERIODONTITIS

4.1 | Background

4.1.1 | Prevalence of respiratory diseases and periodontitis

Periodontitis and respiratory diseases, including chronic conditions (chronic obstructive pulmonary disease [COPD], asthma, obstructive sleep apnea [OSA]) and acute conditions (community-acquired pneumonia [CAP], COVID-19) are highly prevalent diseases, with epidemiological associations among them, and with multiple associated comorbidities. In 2019, lower respiratory tract infections and COPD were in the top 10 diseases inducing long-term disabilities (GBD 2019 Diseases and Injuries Collaborators, 2020), thereby significantly impacting public health. Indeed, 251 million patients were diagnosed with COPD in 2016 worldwide, and it is expected to become the third highest cause of mortality by 2030 (GBD 2015 Chronic Respiratory Disease Collaborators, 2017). Periodontitis affects 45%–50% of adults worldwide, and its severe forms are estimated to affect 796 million people (95% uncertainty interval [UI]: 671–930 million) (Bernabe et al., 2020). Periodontitis significantly impacts oral-health-related quality of life and is considered the main cause of tooth loss. Moreover, it has been linked to several systemic diseases, and successful treatment has been shown to reduce systemic inflammation (Orlandi et al., 2022).

4.1.2 | Mechanisms underpinning the relationship between respiratory diseases and periodontitis

Periodontitis is a chronic inflammatory disease caused by microbial dysbiosis and an imbalance between the bacterial insult and the host response, due to alterations in the abundance or influence of individual species within the polymicrobial community (Hajishengallis & Lamont, 2021). Several hypotheses have been proposed to explain the links between periodontitis and respiratory diseases. Among them, the role for oral microorganisms that can be aspirated with oral secretions, exacerbating pulmonary inflammation and endothelial dysfunction, has been proposed (Hasegawa et al., 2014; Imai et al., 2021). In addition, modifications of the oral and dental plaque/biofilm have been suggested to play a role by several studies (Wu et al., 2017). Other indirect mechanisms, notably the low-grade inflammation associated with periodontitis and the impact of cytokines on pulmonary epithelial cells, have been proposed to exacerbate respiratory diseases. Furthermore, periodontitis and respiratory diseases share some common risk factors, including smoking, obesity and diabetes, that should be considered in order to decipher the underlying biological mechanisms involved in the association (Hajishengallis, 2022).

4.1.3 | Outcomes of the systematic review (Molina et al., 2023): Association studies

COPD and periodontitis

A total of 34 studies (16 cross-sectional, 15 case–control, three cohort studies [two prospective and one retrospective]) evaluated the association between COPD and periodontitis (Molina et al., 2023). A significant association between periodontal status and COPD was observed in 13 cross-sectional/case–control studies and in one prospective cohort study. Four investigations reported significant associations only for specific subsets of the study sample, such as former smokers versus never smokers/current smokers, or smokers versus non-smokers. Similarly, five studies identified significant associations only between COPD and certain stages of periodontitis severity (moderate vs. mild or severe periodontitis) or specific periodontal variables.

A meta-analysis with non-adjusted odds ratios (ORs) showed a statistically significant association between COPD and periodontitis ($n = 12$, OR = 3.11, 95% CI: 2.45–3.93, $p < .001$), with statistically significant ($p < .001$) heterogeneity (using random effects method). A meta-analysis with adjusted ORs demonstrated a statistically significant association between COPD and periodontitis ($n = 12$, OR = 1.28, 95% CI: 1.16–1.42, $p < .001$), without significant heterogeneity ($p = .148$) (using fixed effect method). The interpretation of these ORs may be affected by different factors, such as the age of onset of COPD in the study population, the deterioration rate and other confounders, including smoking. As a reference, the OR of COPD for smokers is 6.3 (95% CI: 4.2–9.5) (Lokke et al., 2006).

A meta-analysis of the effect of periodontitis on the functional capacity of the lungs [(FEV1/FVC) × 100] demonstrated a significant effect, with periodontitis patients presenting a 4.94% lower FEV1/FVC × 100 ($n = 4$, 95% CI: −7.29 to −2.59, $p < .001$), with statistically significant heterogeneity ($p < .001$). The relevance of this 5% lower functional capacity of the lungs in periodontitis patients remains to be established. As a reference, a yearly decrease of 0.3% in functional capacity of the lungs has been reported in patients with atopy (Gottlieb et al., 1996) or a 0.16% yearly in smokers (Bohadana et al., 2006).

Asthma and periodontitis

A total of 19 studies (7 cross-sectional, 9 case–control, 3 cohort) evaluated the association between asthma and periodontitis (Molina et al., 2023). Two cohort studies observed a higher incidence of periodontitis in asthma patients, and six cross-sectional or case–control studies supported the association between both diseases. Six studies reported associations only for certain periodontal variables or for degrees of periodontitis severity. Four studies did not find any association or identified periodontitis as a protective factor for asthma. One cohort study identified periodontitis as a protective factor as well, associated with reduced exacerbation risk in adults.

Nine cross-sectional studies were included in the meta-analyses. No statistically significant associations, both in the unadjusted model (OR = 1.71, 95% CI: 0.84–3.47, $p = .136$; $I^2 = 95.2$, $p < .001$) and in the adjusted model (OR = 1.53, 95% CI: 0.82–2.86, $p = .181$;

$I^2 = 94.6$, $p < .001$), were observed. When only cohort studies were considered, no association was seen (OR = 1.05, 95% CI: 0.83–1.32, $p = .342$; $I^2 = 98.1$, $p < .001$).

OSA and periodontitis

Out of the 12 selected studies (7 cross-sectional, 5 case–control), a significant association between periodontal status and OSA was described in 10 investigations, while 2 studies did not identify any significant association between the two conditions (Molina et al., 2023).

Data from six studies were included in meta-analyses, revealing a statistically significant association in both unadjusted (OR = 3.66, 95% CI: 1.05–12.75, $p = .001$; $I^2 = 95.3$, $p < .001$) and adjusted models (OR = 1.65, 95% CI: 1.21–2.25, $p = .001$; $I^2 = 86.5$, $p < .001$).

CAP and periodontitis

Two studies (one case–control, one cohort) evaluated the association between periodontitis and CAP (Molina et al., 2023), observing an association between CAP and moderate/severe periodontitis, and an increased risk of mortality from pneumonia in subjects with higher numbers of teeth with periodontal pockets >4 mm (in ≥10 teeth), when compared with subjects with fewer pockets (in ≤9 teeth). Owing to the limited available evidence, no meta-analyses could be performed.

COVID-19 and periodontitis

Five studies (two cross-sectional, two case–control, one cohort) were identified (Molina et al., 2023), four of them reporting a significant association between periodontitis and COVID-19 or the risk for COVID-19-associated complications, and one of them observing this association only in obese or overweight patients. One study found no significant association between periodontal status and COVID-19.

Different meta-analyses were performed: no association was found with COVID-19 infection (OR = 3.45, 95% CI: 0.36–33.56, $p = .286$) or with hospital admission (OR = 5.76, 95% CI: 0.15–216.99, $p = .344$). Conversely, associations were found with the need for assisted ventilation (OR = 6.24, 95% CI: 2.78–13.99, $p < .001$) and with COVID-19 mortality (OR = 2.26, 95% CI: 1.36–3.77, $p = .002$).

4.1.4 | Outcomes of the systematic review (Molina et al., 2023): Intervention studies

Two studies (one RCT and one controlled clinical trial [CCT]) evaluated the effect of periodontal therapy on COPD, demonstrating the beneficial effects of periodontal treatment on lung function and on the incidence of exacerbations in subjects with periodontitis and COPD, after up to 24 months of follow-up (Kucukcoskun et al., 2013; Zhou et al., 2014).

A "propensity-matched" cohort study, evaluating the impact of periodontal treatment on asthma, observed a lower incidence of hospitalization for adverse respiratory events and a reduced all-cause mortality in asthmatic patients who had received periodontal therapy versus controls (Shen et al., 2017).

A nationwide, population-based cohort study on the impact of periodontal therapy on the incidence of CAP observed that periodontally treated patients had a reduced risk of developing CAP versus patients not receiving therapy (Yang et al., 2020).

No intervention studies were identified for OSA and COVID-19.

4.2 | Objectives of the WONCA Europe–EFP Workshop on the association between respiratory diseases and periodontitis

The objective of the present WONCA Europe–EFP Workshop was to summarize the available evidence on the associations between periodontitis and the most frequent respiratory diseases, either chronic (COPD, asthma, OSA) or acute (CAP, COVID-19), to assess the impact of periodontal therapy on the progression and complications associated with respiratory diseases and to provide recommendations for family doctors and dental practitioners. The current consensus report is based on the 2012 Joint EFP/AAP Workshop consensus (Linden & Herzberg, 2013), a review performed for a special issue of *Periodontology 2000* (Mammen et al., 2020) and the systematic review by Molina et al. (Molina et al., 2023).

4.3 | Summary of evidence for the association between respiratory diseases and periodontitis

4.3.1 | Chronic obstructive pulmonary disease and periodontitis

Do people with periodontitis have a greater risk of having/developing COPD?

People with periodontitis are at increased risk of having/developing COPD, as demonstrated in a meta-analysis (adjusted ORs: $n = 11$, OR = 1.33, 95% CI: 1.20–1.47) (Molina et al., 2023). In addition, a meta-analysis of the effects of periodontitis on the functional capacity of the lungs [(FEV1/FVC) × 100] found a statistically significant effect, with periodontitis patients presenting 4.94% lower FEV1/FVC × 100 ($n = 4$, 95% CI: −7.29 to −2.59) (Molina et al., 2023). This 5% reduction in functional capacity of the lungs is considered to be highly relevant because, for example, the deterioration rate in patients with atopy has been established as 0.3% annually (Gottlieb et al., 1996) or 0.16% in smokers (Bohadana et al., 2006). The interpretation of the reported data may be affected by different factors such as the age of onset of COPD in the study subjects, the deterioration rate, smoking status, obesity and so on.

Do people with periodontitis and COPD experience greater complications of their COPD?

No association has been observed between periodontal status and increased risk of COPD exacerbations or with the occurrence of fatal and non-fatal COPD-related events. However, this evidence is derived from only three studies (Baldomero et al., 2019; Barros

et al., 2013; Liu et al., 2012), with a cross-sectional design and a limited baseline characterization of COPD patients. Prospective studies are needed to be performed in different clinical settings.

Can the treatment of periodontitis improve lung function and reduce the incidence of complications in COPD patients?

Periodontal therapy, consisting on oral hygiene instructions (step 1), subgingival instrumentation (step 2) and supportive periodontal therapy (step 4, e.g., every 6 months), has beneficial effects in terms of a reduced number of exacerbations and improved lung function, with higher values of FEV1/FVC for up to 24 months (Kucukcoskun et al., 2013; Zhou et al., 2014). These results should be interpreted with caution because of the evident limitations of sample size, among others.

4.3.2 | Asthma and periodontitis

Do people with periodontitis have a greater risk of having/developing asthma?

Evidence for the association between periodontitis and asthma is inconsistent between studies. Limitations of the selected studies include the young age of patients and definitions of asthma, and control of confounders complicate the interpretation of the findings.

Do people with periodontitis and asthma experience greater complications of their asthma?

Evidence for any impact of periodontitis on asthma complications is limited.

Can the treatment of periodontitis reduce the incidence of complications in asthma patients?

Again, evidence for any impact of the treatment of periodontitis on asthma complications is limited.

4.3.3 | Obstructive sleep apnea and periodontitis

Do people with periodontitis have a greater risk of having/developing OSA?

Periodontitis has been linked with a higher prevalence of OSA diagnosis, in 10 out of the 12 retrieved studies. A meta-analysis has shown a statistically significant association ($n = 6$, OR = 1.65, 95% CI: 1.21–2.25, $p = .001$; $I^2 = 86.5$, $p < .001$) between the two conditions.

Do people with periodontitis and OSA experience a more severe form of OSA?

A case–control study (Nizam et al., 2016) reported that periodontitis correlated with the severity of OSA (number of apneas, duration of apneas, mean apneas).

Can the treatment of periodontitis reduce the severity of OSA?

There is no evidence for the effect of periodontal therapy on the severity of OSA in OSA patients.

4.3.4 | Community-acquired pneumonia and periodontitis

Do people with periodontitis have a greater risk of suffering/developing CAP?

The available evidence is limited, as only one case–control study is available, reporting that moderate/severe forms of periodontitis are significantly associated with CAP, and those patients have up to a 3.6-fold higher chance of suffering from CAP when compared with healthy patients or those with mild forms of the disease (De Melo Neto et al., 2013).

Do people with periodontitis and CAP experience greater complications of their pneumonia?

The available evidence is limited, as just one cohort study in an elderly cohort reported a significantly increased risk of pneumonia-associated death in the presence of ≥10 teeth with periodontal pockets >4 mm (hazard ratio [HR] = 3.9, 95% CI: 1.1–13.9), when compared to subjects with <9 pockets (Awano et al., 2008).

Can the treatment of periodontitis reduce the incidence of CAP or CAP-related complications?

The available evidence is limited in CAP patients, with just one study reporting that periodontal treatment is associated with a reduced risk of CAP (L. C. Yang et al., 2020). There is no evidence on the effects of periodontal therapy on CAP-related complications.

4.3.5 | COVID-19 and periodontitis

Do people with periodontitis have a greater risk of suffering more severe forms of COVID-19?

Current evidence supports a positive and significant association between periodontitis and a diagnosis of SARS-CoV-2 infection (in four out of five retrieved studies). In one cohort study, when stratified by weight, it appeared that the association was stronger for overweight or obese subjects in comparison to normal-weight patients (Larvin et al., 2021). Data from two studies reported that advanced forms of periodontitis (periodontitis in stages III/IV) have been associated with a higher incidence and severity of COVID-19 and its complications, such as COVID-19 pneumonia, hospital admission, ICU admission, need for assisted ventilation or death due to COVID-19 (Gupta et al., 2021; Marouf et al., 2021). Meta-analyses have shown significant associations between periodontitis with a need for assisted ventilation (OR = 6.24, 95% CI: 2.78–13.99, $p < .001$) and with COVID-19-associated mortality (OR = 2.26, 95% CI: 1.36–3.77, $p = .002$).

Can the treatment of periodontitis reduce COVID-19 severity and its complications?

There is no evidence for any effect of periodontal therapy on COVID-19 severity or its complications.

4.4 | Guidance: Respiratory diseases–periodontitis

4.4.1 | Guidance for family doctors: should family doctors refer patients with respiratory diseases for a comprehensive oral health assessment?

- Based on the previously presented limited evidence, including the association between COPD and periodontitis, and the foreseeable improvements resulting from periodontal therapy, it is recommended that family doctors refer patients with COPD, or at risk of developing COPD, for an oral/periodontal health examination. Furthermore, family doctors should refer/recommend smokers with COPD or at risk of developing COPD for an oral/periodontal health examination.
- Considering the documented oral side effects of asthma treatments, a referral/ recommendation for a comprehensive oral/ periodontal health examination may be appropriate for some patients with asthma.
- Patients with OSA should be referred for a comprehensive oral/ periodontal examination in order to evaluate their oral/periodontal health, because of the reported association between OSA and periodontitis, and for the use of positive pressure airway machines or oral appliances in its treatment.
- A referral/recommendation of patients with a history of CAP, for a comprehensive oral/periodontal health examination, may be appropriate, based on the limited evidence available.

4.4.2 | Guidance for family doctors and OHPs: should family doctors and OHPs provide patients with respiratory diseases with any specific oral health care recommendations?

Chronic obstructive pulmonary disease (COPD) patients

- COPD and periodontitis share important risk factors, tobacco smoking being the most relevant. Smoking cessation must be promoted in all smokers in dental care settings, directly or by a referral to the family doctor. This will decrease the risk of developing both diseases and their associated comorbidities.
- Owing to the negative impact of socio-economic factors on these conditions, a significant proportion of patients may not have access to proper medical and/or dental care, and outreach programmes should be implemented.
- Specifically for OHPs, education in adequate oral hygiene habits should be provided to COPD patients by OHPs, including information on oral hygiene devices/products, techniques and brushing frequency (Sanz, Herrera, et al., 2020). A brushing frequency of less than once per day has been significantly associated with frequent exacerbations of COPD (Liu et al., 2012). In addition, screening, diagnosis and eventually treatment of periodontal conditions should be carried out as early as possible.

Asthma patients

The potential impact on oral/periodontal health of some treatments (e.g., corticosteroid inhalers) may need to be discussed with asthma patients, especially if adequate oral hygiene is lacking.

Obstructive sleep apnea patients

- Since obesity is an established risk factor (OR = 4.4, 95% CI: 1.4–13.2) for OSA patients (Schafer et al., 2002), strategies for weight loss and healthy life styles should be recommended in both primary care and dental care settings.
- A discussion with the patient on the potential side effects on oral health (e.g., dry mouth, increase in periodontal inflammation, increase/alteration in biofilm formation) of continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) machines may be necessary.
- A discussion with the patient on the potential side effects on oral health of oral appliances may be necessary. Among oral appliances, the following appliances used to treat mild or moderate OSA and snoring should be considered: mandibular advancement devices (MADs), mandibular advancement splints (MASs), mandibular repositioning appliances (MRAs) and tongue-retaining devices (TRDs) (American Thoracic Society, 2018).
- For young patients, an orthodontic evaluation may be relevant in certain situations.

Patients with a history of community-acquired pneumonia

No specific recommendations should be given to patients with a history of CAP.

Patients with COVID-19, or with a history of severe COVID-19

For patients with COVID-19:

- Toothbrushes and/or other oral hygiene devices (interproximal brushes, tongue scrapers, etc.) should be kept separate from those of their relatives or co-inhabitants.
- Certain antiseptic mouth rinses (those with a demonstrated impact on salivary viral load in in vivo studies, such as cetylpyridium chloride) may be considered (Alemany et al., 2022; Barrueco et al., 2022; Smeets et al., 2022).

Patients with a history of severe COVID-19 (e.g., who required hospitalization):

- Patients should be referred for a comprehensive oral health assessment, in order to evaluate the consequences of ICU syndrome, to screen for periodontitis or to detect oral lesions associated with COVID-19.

The role of family doctors and oral health professionals in controlling COVID-19 in primary care and dental care settings

Preventive measures recommended by health authorities should be respected in primary medical and dental care settings, and constantly updated. Primary medical and dental care settings are safe

environments provided preventive measures are followed thoroughly and according to local recommendations. Therefore, visits to primary medical and dental settings should not be delayed or neglected.

4.4.3 | Guidance for healthcare funders

Oral/periodontal care should be considered, on a systematic basis, for all patients diagnosed with COPD, since it can greatly improve the quality of life, morbidity and mortality and health costs. Health insurance companies and/or public health systems should be able to support oral/periodontal screening and diagnosis for patients with COPD, and also subsequent treatment. WHO Resolution (WHO, 2021) urges Member States to address key risk factors for oral diseases that are shared with other NCDs, and that oral healthcare interventions should be included in universal health coverage programmes.

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ETHICS STATEMENT

Due to the nature of the project, concerns for ethics in research are not applicable.

DATA AVAILABILITY STATEMENT

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

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