INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

PREDICTORS OF TOOTH LOSS DURING LONG-TERM PERIODONTAL MAINTENANCE: AN UPDATED SYSTEMATIC REVIEW

Trabalho submetido por
Rui Pedro Matos de Carvalho
para a obtenção do grau de Mestre em Medicina Dentária

setembro de 2021

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Trabalho orientado por
Prof. Doutor José João Mendes

e coorientado por
Prof. Doutor Leandro Chambrone e Mestre João Botelho

setembro de 2021

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Abstract

Aim: To evaluate the risk factors / predictors of tooth loss in patients with periodontitis who underwent periodontal therapy and long-term periodontal maintenance (PM).

Material & Methods: PUBMED, CENTRAL, EMBASE, Web of Science, LILACS and Google Scholar databases were searched until September 2020. Studies limited to periodontitis patients who underwent active periodontal therapy and followed a regular PM program with at least 5 years of follow-up were considered for inclusion. Studies were included if data on tooth loss during PM were reported. Random effects meta-analyses of number of tooth loss per patient per year were conducted.

Results: Thirty-six papers regarding thirty-three studies were included, with three prospective and 30 retrospective trials. Subgroup meta-analysis showed no difference between prospective and retrospective studies, with an average of 0.1 tooth loss per year per patient ($p<0.001$). Maxillary and molar teeth were more susceptible to be extracted during long-term PM. Baseline characteristics (smoking, *diabetes mellitus*, cardiovascular disease, being male, and teeth with furcation lesions) showed no significance as predictor of tooth loss through meta-regression. The percentage of tooth loss due to periodontal reasons ranged from 0.45% to 14.4%. Individual outcomes in each study evidenced different patient-related factors (age and smoking) and tooth-related factors (i.e., tooth type and location) were associated with tooth loss during PM. All analyses showed complete homogeneity ($I^2=0\%$).

Conclusion: Most patients undergoing long-term PM have not lost teeth. Long-term PM causes the loss of 1 tooth per patient every 10 years. Additional prospective trials may confirm these results.

Keywords: Periodontal Disease; Periodontitis; Long-term Maintenance; Tooth loss.

Resumo

Objetivos: Avaliar os fatores de risco / preditivos para a perda de dentes em pacientes periodontais tratados e com uma manutenção periodontal de, pelo menos, 5 anos.

Materiais e Métodos: A pesquisa foi realizada nas bases de dados *PUBMED, CENTRAL, EMBASE, Web of Science, LILACS* e *Google Scholar* com data de publicação até setembro de 2020. Apenas estudos que incluíram pacientes que realizaram terapia periodontal ativa e seguiram uma terapia periodontal de suporte (TPS) por um período mínimo de 5 anos de seguimento foram considerados elegíveis para esta revisão. Os estudos foram incluídos se reportassem dados sobre o número de dentes perdidos durante a TPS. Foi realizada meta-análise de incidência para o número de dentes perdidos por paciente por ano.

Resultados: Trinta e seis artigos relativos a 33 estudos foram incluídos, 3 estudos prospetivos e 30 retrospetivos. A meta-análise de subgrupo revelou não existirem diferenças entre os estudos retrospetivos e prospetivos, com uma média de 0.1 dentes perdidos por paciente por ano ($p<0.001$). Os dentes superiores e os molares apresentaram maior risco de serem perdidos durante a TPS. Características como *diabetes mellitus*, doença cardiovascular, sexo, e dentes com lesão de furca não demonstraram valor preditivo significativo de perda dentária através de meta-regressão. A idade, hábitos tabágicos e fatores relacionados com o dente (tipo de dente e localização) foram associados com perda dentária durante a TPS. Todas as análises demonstraram homogeneidade completa ($I^2=0\%$).

Conclusão: A maioria de pacientes que cumpriu um programa de TPS prolongada não perdeu qualquer dente. Em média, a TPS prolongada leva à perda de 1 dente por paciente a cada 10 anos. Estudos prospetivos adicionais poderão confirmar a consistência destes resultados.

Palavras-chaves: Doença Periodontal; Periodontite; Manutenção Periodontal, Perda dentária

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List of Abbreviation

APT – Active Periodontal Therapy

IL - Interleukin

IPT – Intensive Periodontal Therapy

NSPT – Non-Surgical Periodontal Treatment

PD – Periodontal Disease

PM – Periodontal Maintenance

PPD – Periodontal Probing Depth

PT – Periodontal Treatment

RCT – Randomized Clinical Trial

SPT – Surgical Periodontal Treatment

TNF - Tumor Necrosis Factor

TPS – Terapia Periodontal de Suporte

UPS – Ubiquitin Proteosome System

I. INTRODUCTION

1. PERIODONTITIS

Periodontal disease (PD) is a clinical entity that comprises a group of diseases affecting the periodontium (among which are gingivitis, periodontitis, necrotizing periodontal conditions, periodontitis as a manifestation of systemic disease, periodontal abscesses and endodontic-periodontal lesions) (Armitage, 1999; Caton et al., 2018; Lamont et al., 2018). Specifically, periodontitis is one of the most prevalent oral conditions worldwide (Marcenes et al., 2013), and was responsible for an estimated loss of $154.06B in the United States of America and €158.64B in Europe, in 2018 (Botelho et al., 2021).

Periodontitis is a chronic and inflammatory non-communicable disease, compromising the integrity of the periodontium, resulting in deep periodontal crevices (also known as periodontal pocket), attachment loss and alveolar bone loss (American Academy of Periodontology [AAP], 2001; De Wet et al., 2018; Hajishengallis, 2015; Highfield, 2009; Weinmann, 1952).

The existence of numerous classifications for periodontitis and clinical measures make the interpretation and homogeneity of epidemiological data complex (Lamont et al., 2018). At a global scale, the Global Burden of Disease (1990-2010) ranked periodontitis as the sixth most prevalent disease (Kassebaum et al., 2014; Marcenes et al., 2013; Nazir, 2017). In Portugal, the Study of Periodontal Health in Almada-Seixal documented a 59.9% prevalence of periodontitis, with 46.2% of moderate-to-severe cases in the Southern Lisbon Metropolitan Area (Botelho et al., 2019). The prevalence of periodontitis is increased in men and age-dependent (Ebersole et al., 2016; Eke et al., 2016). Also, the periodontal-systemic health link has been extensively researched in the past decades (Hajishengallis & Chavakis, 2021).

To manage this condition, periodontal patients require a rigorous protocol of consults towards dental plaque removal via non-surgical and/or surgical approaches, called periodontal treatment (PT). Several clinical difficulties arise during PT (that will be introduced later), yet the lack of adherence proves to be the major challenge because this negligent behavior jeopardizes the success of PT and furthering this disease (Ramseier, Suvan, et al., 2015).

1.1. Clinical Manifestations

The periodontium is comprised of soft and hard tissues (Darveau, 2010; Nibali, 2017). The space formed between the epithelial and teeth surface – designated as gingival sulcus – is surrounded by the gingival crevicular fluid (an osmotic capillary transudate containing leukocytes, antibodies, cytokines, oral bacteria, enzymes and tissue-degradation products) (Darveau, 2010; Donos, 2017). The presence of an inflammatory exudate on the junctional epithelium is always present, revealing the existence of a subclinical inflammation signal, even in a physiological state (Brecx et al., 1987).

The accumulation of dental plaque is inevitable, and mainly occurs at stagnant sites, where tooth brushing is ineffective (Marsh, 2004). Biofilm and bacteria can undermine the junctional epithelium resulting in further subgingival dissemination of bacteria (Donos, 2017). Thus, this physiological state can be disrupted by the presence of subgingival bacterial products that lead to the release of hosts' inflammatory mediators (Hajishengallis, 2015). As a consequence, the connective tissue is destroyed along with gingival inflammation, deepening of gingival sulcus and creation of pathological periodontal pockets, allowing bacteria spread along the root surface (Nibali, 2017; Page & Kornman, 1997; Tonetti et al., 2018).

Periodontitis is therefore characterized by the loss of supporting periodontal tissue, clinically seen as deep periodontal pockets, and may eventually lead to tooth loss if not treated (Darveau, 2010; Papapanou et al., 2018; Sanz et al., 2020) (Figure 1).

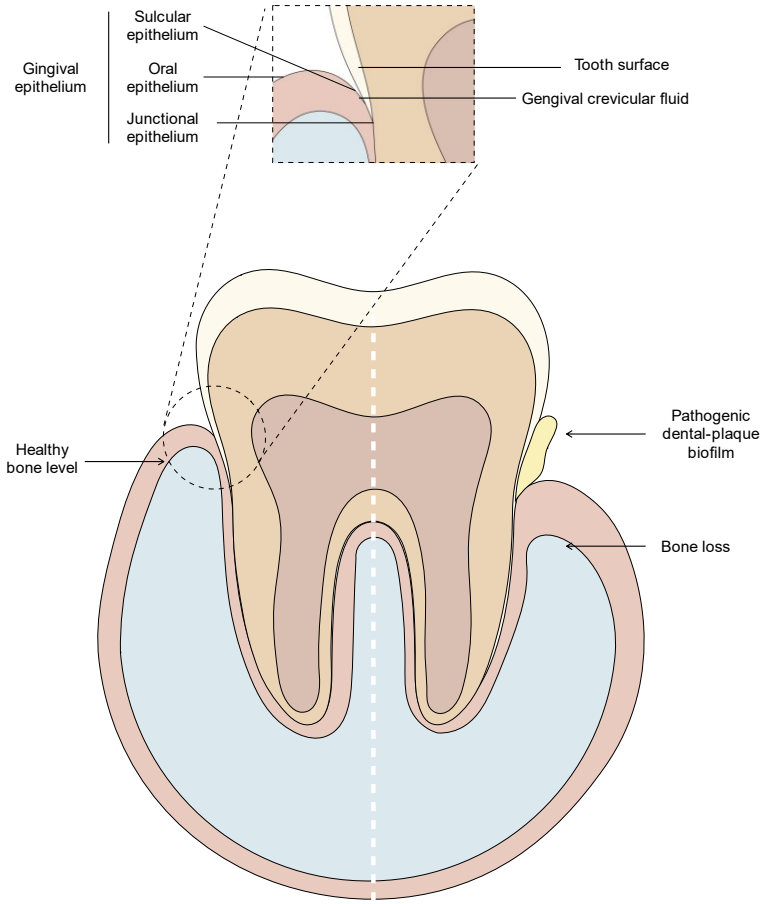

Figure 1 | Schematic representation of periodontitis. Healthy periodontal insertion (left to the dotted white line) where tooth is supported by connective tissue and alveolar bone. Specialized junctional epithelium is connected to the tooth surface, covered by the oral epithelium. The space formed between the tooth and the epithelial surface is designated as sulcus and is filled with the gingival crevicular fluid. Local effects of periodontitis (right to the dotted white line) show a destruction of periodontal connective tissue and alveolar bone by the accumulation of pathogenic dental-plaque biofilm on tooth and tooth root surface, resulting in the most common cause for tooth loss. Original image.

Beyond the local impact in the oral cavity, this local periodontal inflammatory reaction may trigger a bulk of systemic inflammatory responses (Hajishengallis & Lamont, 2012). Periodontitis hence exerts its effect on other chronic conditions such as *diabetes mellitus* (Preshaw et al., 2012; Simpson et al., 2015), obesity and metabolic syndrome (Genco & Borgnakke, 2013), cardiovascular diseases (Muñoz Aguilera et al., 2020), cancer (Corbella et al., 2018), rheumatoid arthritis (Hussain et al., 2020) and adverse pregnancy outcomes (Sanz & Kornman, 2013). Also, periodontitis has been associated with polycystic ovary syndrome (Machado, Escalda, et al., 2020), bacterial vaginosis (Escalda et al., 2021), and more recently, with increased risk of complications from Coronavirus Disease 19 (Marouf et al., 2021).

1.2. Pathophysiology

The dental plaque is a rich milieu, located at the gingival sulcus, with up to 500 different bacterial species (Darveau, 2010). In the periodontium, the transition from health to disease occurs through a radical shift from a symbiotic (mostly of Gram-positive facultative bacterial genera) to a dysbiotic microbial community (mainly anaerobic Gram-negative species) (Darveau, 2010; Hajishengallis, 2015; Marsh, 1994).

This diversity may pose a clinical challenge for PT, being one among several reasons why conventional therapy is not entirely effective (Socransky & Haffajee, 2002).

Histologically, the periodontium lacks a large mucous layer to prevent the contact between the microbial community and the epithelial cell surface. The junctional epithelium has desmosomes and gap junctions that contribute to its porosity, and in periodontitis an appropriate orchestrated response is needed against the dental plaque biofilm (Darveau, 2010; Meyle & Chapple, 2015). In this coordinated reaction, the expression of E-selectin, intercellular adhesion molecules and interleukin 8 (IL-8), promotes the passage of neutrophiles to the gingival crevice, where they form a barrier between the host tissue and the dental plaque biofilm (Darveau, 2010).

Clinically, periodontitis is frequently associated with the progression of an instituted and untreated reversible gingivitis (Lang et al., 2009; Nibali, 2017). The biofilm accumulation favors the growth of particular bacterial species, such as *Fusobacterium nucleatum* or *Porphyromonas gingivalis*, capable of eliciting a more intense host response (Meyle & Chapple, 2015). As a consequence, a self-perpetuating cycle is established, where dysbiosis and inflammation underpin each other forming a positive feedback loop (Hajishengallis, 2015; Meyle & Chapple, 2015).

A triad of oral anaerobic bacteria, *Porphyromonas gingivalis, Treponema denticola and Tannarella forsythia* (designated as the red complex), have been traditionally considered as the causal agent for periodontitis based on its virulence and robust association to worse periodontal states (Darveau, 2010; Hajishengallis, 2015). However, other complexes are involved in the periodontitis pathophysiology, where this condition results rather from a polymicrobial synergy and dysbiosis (Hajishengallis, 2015).

Moreover, the pathogenic role of other microorganisms in periodontitis, such as viruses and amoebas is also emerging, either as primary agents of host immune cells or as co-

infectors alongside with bacteria plotting to dysregulate host-defense system (Bao et al., 2020; Meyle & Chapple, 2015).

While bacteria play a primary role in the periodontal disease onset, risk factors (patient-related factors) can impact the clinical presentation and progression of periodontitis (Heitz-Mayfield, 2005; Meyle & Chapple, 2015).

1.3. Risk factors for periodontitis

Several modifiable and non-modifiable risk factors have been suggested for periodontitis, and distinctive hallmarks may lead to different clinical manifestations (AlJehani, 2014; Genco & Borgnakke, 2013; Nazir, 2017; Stabholz et al., 2010; Van Dyke & Sheilesh, 2005).

Dental plaque accumulation, the host immune system and specific destructive processes can jointly be considered periodontitis' etiological factors, although neither microbial dysbiosis and dental plaque accumulation will solely develop periodontitis in prone hosts (Hajishengallis, 2015; Slots, 2017).

Nevertheless, the host immune system plays an important role on the pathogenesis of periodontitis, not only is periodontitis associated with a dysregulated immune response, genetic predisposition can also influence periodontitis onset as most genes considered to be responsible for periodontitis are also linked with immune response (Ebersole et al., 2016; Genco & Borgnakke, 2013; Hajishengallis, 2015; Stabholz et al., 2010; Van Dyke & Sheilesh, 2005).

A widely studied example of host immune dysregulation and its effect on periodontitis is the *diabetes mellitus* link with periodontitis. The levels of IL-1β, IL-6, prostaglandin E2 and tumor necrosis factor α (TNF-α) are highly expressed in type 1 and 2 *diabetes mellitus* when compared with non-diabetic patients, resulting in higher tissue destruction and increasing the risk of periodontitis onset and progression (Genco & Borgnakke, 2013; Nascimento et al., 2018). Notwithstanding, PT revealed a positive impact on the metabolic control, reducing the Haemoglobin A1c levels and systemic inflammation (Baeza et al., 2020; D'Aiuto et al., 2018; Madianos & Koromantzos, 2018).

Lifestyle habits, such as smoking, can also contribute to the dysregulation and increased risk for periodontitis onset and progression (Leite et al., 2018). Mechanistically, nicotine causes an increase in the TNF-α levels present in crevicular fluid by patients' macrophages contributing to connective tissue and periodontal bone destruction (Genco & Borgnakke, 2013). Also, the rise IL-1 and IL-6 levels lead to an increase bone resorption thru the upturn in the ratio between receptor activator of nuclear factor-κβ ligand and its inhibitor osteoprotegerin (Leite et al., 2018).

Furthermore, the dysregulation of the ubiquitin-proteosome system (UPS) is another conceivable factor for periodontitis, as the UPS exacerbation in the periodontium nurtures proteins destruction that can ultimately result in periodontium tissue destruction (Machado, Carvalho, et al., 2020).

Other patient-related risk factors such as age, gender, obesity and metabolic syndrome, lifestyle habits (alcohol, oral hygiene), medication, stress, socioeconomic status and educational levels can contribute to dysregulate hosts immune system and increase the risk for periodontitis onset and progression (AlJehani, 2014; Eke et al., 2016; Genco & Borgnakke, 2013; Nazir, 2017; Stabholz et al., 2010).

2. PERIODONTAL TREATMENT

As presented, PT aims to eradicate the causal agents of periodontal disease to halt its progression and mitigate symptoms (Manresa et al., 2018). As well, PT serves to educate and guide patient's behavior towards healthy periodontal lifestyle habits (De Wet et al., 2018; Graziani et al., 2017; Manresa et al., 2018; Slots, 2017).

The clinical regimen of PT reveals to be effective and with good prognosis if early implemented (Renvert & Persson, 2016; Slots, 2017; Trombelli et al., 2015). Furthermore, oral health-related quality of life, an impactful patient-centered outcome (Fischer et al., 2020; Needleman et al., 2004), is deteriorated in periodontitis but is effectively restored after non-surgical PT (Botelho et al., 2020; Buset et al., 2016).

Recently, Tonetti and Sanz (2019) proposed a new four-based steps algorithm to aid periodontal diagnosis method based on the new staging and grading of the 2018 case definition (Figure 2). Then, confirmed periodontal patients have to be informed about the diagnosis, risk factors, treatment alternatives and predicted risk and benefits

(including the option of not treating) as a key pre-requisite to initiate PT (Sanz et al., 2020).

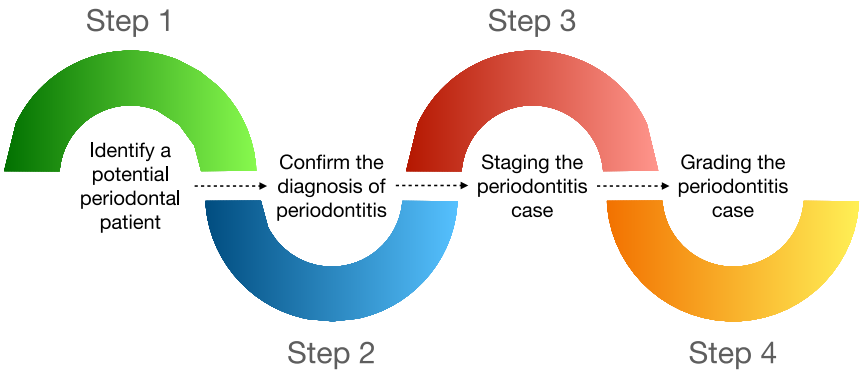

Figure 2 | Algorithm for periodontal diagnosis. An algorithm proposed to aid periodontal diagnosis comprising 4 sequential steps, where (from left to right) the first step consist in identifying a potential patient with periodontitis, follow by the verification of periodontitis diagnosis. Thirdly, determine the stage of periodontitis and fourthly determine the grade of periodontitis (Tonetti & Sanz, 2019).

A model for PT planning was suggested by Salvi et al. (2015) where four sequential phases of treatment should be progressively instituted, upon diagnosis of periodontitis (Figure 3).

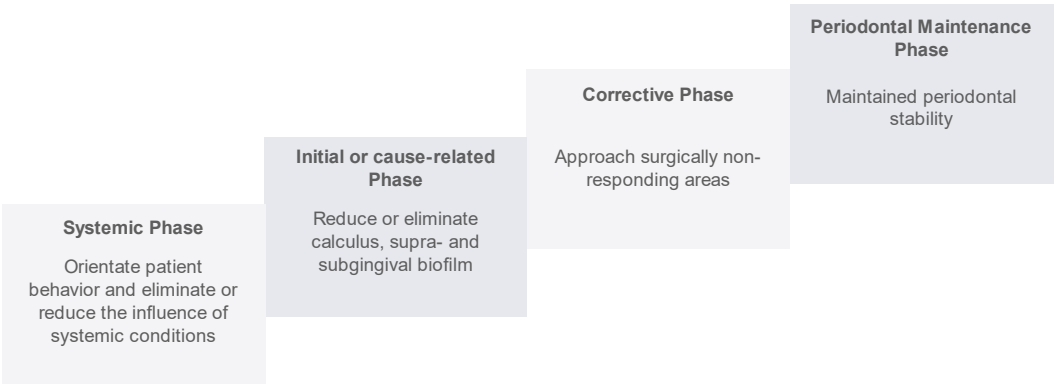

Figure 3 | Proposed model for the stages of PT. Proposed model for periodontal treatment, where different phases were gathered into a sequential procedure. Firstly, systemic phase aims to orientate patient behavior towards periodontal disease and eliminate or reduce the influence of systemic conditions. The second phase, called initial or cause-related phase, intent to reduce or eliminate calculus, supra- and subgingival biofilm. Corrective phase, the third, focuses on the non-responding areas from previous phase in a surgically approach. Finally, the PM phase, where periodontal stability is aimed, preventing the progression or reoccurrence of disease (Adapted from Salvi, Lindhe & Lang (2015)).

Amid this proposed model, active PT (APT) comprises standard procedures that consist of oral hygiene instructions, removal of calculus and biofilm (Step 2 - initial or cause-

related phase), with the use of adjunctive antimicrobials or surgical treatment if necessary (Step 3 - Corrective phase) (Loos & Needleman, 2020). This treatment modality is further introduced in the subsection 2.1.

Other modalities of treatment can also be delivered in periodontitis cases, such as intensive PT (IPT), were a full-mouth disinfection protocol comprehending a subgingival debridement within 24 hours is performed (Quirynen et al., 1995). However, this modality causes a peak of serum IL-6, C-reactive protein and reactive oxide metabolites, as well as a decrease of soluble thrombomodulin that can affect negatively the systemic vascular endothelial function (D'Aiuto et al., 2010; Machado et al., 2021; Tonetti et al., 2007; Ushida et al., 2008).

2.1. Active Periodontal Therapy

To enable the patient to sustain its oral health APT aims to preserve teeth, to avoid disease reoccurrence, to decrease gingival inflammation, to reduce or eliminate deepened pockets and to restore periodontal attachment (Loos & Needleman, 2020; Pihlstrom, 1992).

Several studies showed the effectiveness of APT in improving on periodontal clinical parameters, resulting in a reduction on the mean periodontal probing depth (PPD), average clinical attachment level, mean bleeding on probing and a reduction on tooth loss (Graetz et al., 2015, 2020; Graetz, Plaumann, et al., 2017; Graetz, Sälzer, et al., 2017; Miller et al., 2017; Ramseier et al., 2019; Ramseier, Mirra, et al., 2015; Ravidà et al., 2019; Trombelli et al., 2015; Van der Weijden & Timmerman, 2002).

Different treatment approaches can be applied within APT. Non-surgical PT (NSPT) consists of a subgingival debridement (manual and/or mechanic) with positive effects in both shallow (1-3 mm) and moderate pockets (4-6 mm) (Brayer et al., 1989; Caffesse et al., 1986; Cirino et al., 2019; Deas et al., 2016). However, not at sites/teeth respond equally to NSPT, as well as in deep pockets (≥ 6mm), thus surgical PT (SPT) can be a further alternative (Deas et al., 2016; Graziani et al., 2017). SPT was found to be equally efficiency as NSPT, although it was associated with higher risk of gingival recession (Cirino et al., 2019), and is usually considered the next clinical step when NSPT is not entirely effective as expected (Heitz-Mayfield & Lang, 2013; American Academy of Periodontology [AAP], 2011).

After the active stages of PT, a PM stage follows in order to adequately monitor the progression of periodontitis.

2.2. Periodontal maintenance

Periodontal maintenance (PM), formerly referred as supportive PT, comprehends a systematic personalized visit program according to the patient- and tooth-related factors (AAP, 2001; Lang & Tonetti, 2003).

Maintenance procedures typically include a medical and dental history update, periodontal reevaluation, radiography review, removal of the bacterial flora from crevicular and pocket areas, scaling and root planing where indicated and, if necessary, polishing of the teeth and a reassessment of patient plaque control efficacy (AAP, 2001).

Additionally, PM aims to reduce the reoccurrence of periodontitis through periodic preventive interventions, as periodontal patients have a higher risk of future episodes of disease, usually affecting the same sites (Armitage & Xenoudi, 2016; Echeverría et al., 1996; Fardal et al., 2004; Hirschfeld & Wasserman, 1978; Lang & Tonetti, 2003; Manresa et al., 2018; Tonetti et al., 1998, 2000; Wood et al., 1989). These objectives are reached by preventing the reoccurrence of periodontal disease in previously treated patients, tooth loss incidence and identifying and treating other oral conditions found in a timely way (American Academy of Periodontology [AAP], 1998; Manresa et al., 2018).

When assessing the effectiveness of PM, several studies demonstrate that frequent recall visits contributed to reducing tooth loss by patients over time, loss of periodontal support, clinical progression and the need of retreatment (Albuquerque et al., 2018; L. Chambrone et al., 2010; Goh et al., 2017; Kim et al., 2014; Miyamoto et al., 2010; Ng et al., 2011). In addition, tooth loss experience is prone to occur in a reduced group of high-risk patients (L. A. Chambrone & Chambrone, 2006).

Time interval between PM recall visits should be determined taking into account the overall risk profile and the expected benefit for the patient (Lang & Tonetti, 2003; Manresa et al., 2018). This is based on multiple clinical conditions that should be collectively considered, thus attempting to predict periodontitis progression and tooth loss in treated patients (Lang & Tonetti, 2003; Lang et al., 2015; Manresa et al., 2018).

The Periodontal Risk Assessment for patients in PM is based on six specific parameters defined by Lang and Tonetti (2003): "1) percentage of bleeding on probing, 2) prevalence of residual pockets greater than 4mm (≥ 5mm), 3) loss of teeth from a total of 28 teeth, 4) loss of periodontal support in relation to the patient's age, 5) systemic and genetic conditions, and 6) environmental factors, such as smoking, each of these parameters is evaluated on a low, medium or high-risk scale". The comprehensive analysis of the formed diagram will determine the individualized risk profile and establish the periodicity of PM visits (Lang & Tonetti, 2003).

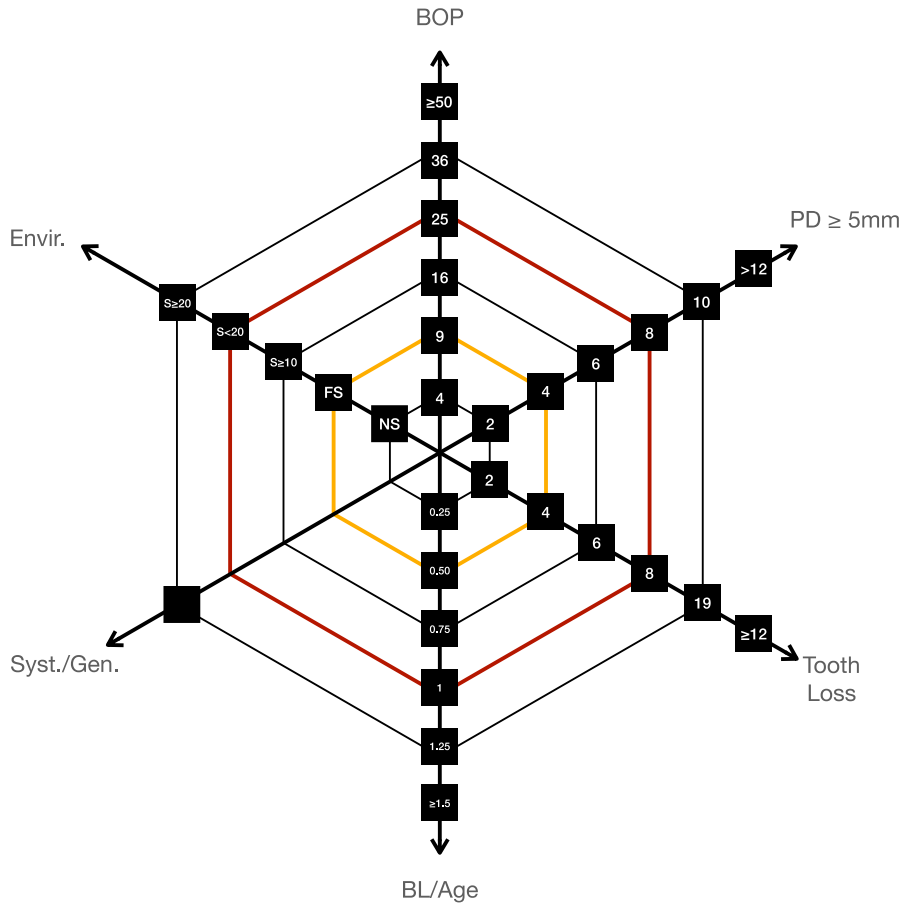

Figure 4 | Periodontal Risk Assessment diagram. This hexagonal diagram provides the patient's risk for progression or reoccurrence of periodontitis. Each risk factor is represented in one vector of the diagram, and all risk factors must be assessed together. (Adapted from Lang, 2003). BOP – Bleeding on Probing; PD – Probing Depth; BL – Bone Loss; Syst. – Systemic; Gen – Genetic; Envir. – Environmental.

The clinical outcomes achieved during PM appear to be influenced by patients-related factors, such as smoking and diabetes, and tooth-related factors, as the type of tooth and arch location (Albuquerque et al., 2018; Bäumer et al., 2011; L. Chambrone et al., 2010; L. A. Chambrone & Chambrone, 2006; Dannewitz et al., 2016; De Beule et al., 2017;

De Wet et al., 2018; Díaz-Faes et al., 2016; Fardal et al., 2016; Goh et al., 2017; Johansson et al., 2013; König et al., 2002; Miyamoto et al., 2010; Nibali et al., 2017, 2018; Pretzl et al., 2018; Ravald & Johansson, 2012). Patient's compliance trough PM programs is also an influential factor to PM efficacy as it is associated with less risk of tooth loss (Eickholz et al., 2008; Kim et al., 2014; Needleman et al., 2018).

In 2010, L. Chambrone et al. (2010) showed that inadequate plaque control, age, gender, initial attachment loss, presence of furcation involvement, baseline tooth mobility and tobacco smoking were positively associated with tooth loss during PM (L. Chambrone et al., 2010). A more recent review analyzed twelve different predictors for tooth loss in periodontitis patients, categorized as patient-level (age, non-compliance, smoking, diabetes, IL-1 polymorphism) and tooth-level factors (bone loss, deep pockets, severe mobility, furcation involvement and molar teeth) that could contribute towards tooth loss during PM (Helal et al., 2019).

2.3. Risk factors for tooth loss during PM

From a clinical point of view, periodontal stability relies on a balanced symbiotic relationship between dental plaque and the host immune system (Lang & Tonetti, 2003). Therefore, the diagnostic process must bear a continuous multilevel evaluation of the risk profile. Risk factors (patient-, tooth-, and site-related) can alter the path of PT as this should be considered to prevent the reoccurrence of periodontal disease progression (Lang & Tonetti, 2003).

Regarding patient-related factors, patients' compliance (Ravald & Johansson, 2012; Saminsky et al., 2015), prevalence of residual pockets >4 mm (De Beule et al., 2017), loss of periodontal support in relation to the patient's age (Nibali et al., 2017, 2018), loss of teeth from a total of 28 teeth (Ravald & Johansson, 2012), smoking (Graetz, Plaumann, et al., 2017; Graetz, Sälzer, et al., 2017; Ravald & Johansson, 2012) and systemic conditions (L. Chambrone et al., 2010) were considered as predictors for tooth loss during PM.

Other factors, such as tooth-related factors, must be taken into consideration, as can be associated with tooth loss. Tooth position in the arch (De Beule et al., 2017; Graetz et al., 2015; Graetz, Sälzer, et al., 2017), furcation involvement (Graetz et al., 2015; Graetz, Sälzer, et al., 2017; Johansson et al., 2013; Nibali et al., 2017, 2018), residual

bone support (Graetz et al., 2015; Graetz, Plaumann, et al., 2017; Miyamoto et al., 2010; Nibali et al., 2018), tooth mobility (Ekuni et al., 2009; Graetz et al., 2015) and type of tooth (single or multi-rooted) can increase the risk of tooth loss during PM.

Also, site-related factors, as probing depth, suppuration and bleeding on probing are also linked with gained risk for tooth loss (De Beule et al., 2017; Miyamoto et al., 2010; Seirafi et al., 2014).

All in all, appraising the risk factors associated with tooth loss during PM still stands out to be of high relevance and to be continuously explored.

3. AIMS

Therefore, we aimed to update the previous version of L. Chambrone et al. (2010) systematic review by revisiting potential predictors of tooth loss among patients who underwent APT and long-term PM. Thus, the following PECO(T) question was proposed to be answered: "What local and systemic risk factors are associated with tooth loss during long-term PM?", with the following statements:

- P (Population): Patients with periodontitis and local or systemic risk factors who suffer tooth loss
- E (Exposure): Local or systemic risk factors
- C (Comparison): Patients with periodontitis without local or systemic risk factors who suffer tooth loss
- O (Outcomes): Tooth Loss
- T (Timing): During long-term PM of, at least, 5 years

II. PREDICTORS OF TOOTH LOSS DURING LONG-TERM PERIODONTAL MAINTENANCE: AN UPDATED SYSTEMATIC REVIEW

This chapter is adapted from:

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SYSTEMATIC REVIEW

Predictors of tooth loss during long-term periodontal maintenance: An updated systematic review

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Abstract

Aim: To evaluate the risk factors / predictors of tooth loss in patients with periodontitis who underwent periodontal therapy and long-term periodontal maintenance (PM).

Material and Methods: PubMed, CENTRAL, EMBASE, Web of Science, LILACS and Scholar were searched up to and including September 2020. Studies limited to periodontitis patients who underwent active periodontal therapy (APT) and followed a regular PM programme with 5 years follow-up minimum were eligible for inclusion in this review. Studies were included if they reported data on tooth loss during PM. Random effects meta-analyses of number of tooth loss per patient per year were conducted.

Results: Thirty-six papers regarding thirty-three studies were included in this review, with three prospective 30 retrospective trials. Subgroup meta-analysis showed no differences between prospective and retrospective studies, with an average of 0.1 tooth loss per year per patient ($p < 0.001$). Maxillary and molar teeth were more susceptible to be extracted during long-term PM. Baseline characteristics (smoking, diabetes mellitus, cardiovascular disease, being male and teeth with furcation lesions) showed no significance as predictor of tooth loss through meta-regression. The percentage of tooth loss due to periodontal reasons ranged from 0.45% to 14.4%. The individual outcomes in each study evidenced different patient-related factors (age and smoking) and tooth-related factors (i.e. tooth type and location) were associated with tooth loss during PM.

Conclusion: The majority of patients undergoing long-term PM have not lost teeth. On average, long-term PM effectively causes the loss of 1 tooth per patient every 10 years. Additional prospective trials may confirm these results.

KEYWORDS
long-term maintenance, periodontal disease, periodontitis, supportive periodontal therapy, systematic review, tooth loss

Rui Carvalho and João Botelho are equally first authors.

Clinical Relevance

Scientific rationale for the study: During periodontal maintenance (PM), different patient- and tooth-related factors may be related with tooth loss. Given the increased amount of evidence, predictors of tooth loss during long-term PM were revisited in a systematically fashion.
Principal findings: On average, long-term PM effectively causes the loss of 1 tooth per patient every 10 years. The individual outcomes in each study evidenced different patient-related factors and tooth-related factors were associated with tooth loss during PM.
Practical implications: Patients at long-term PM have an average of 0.1–0.2 tooth loss per year per patient.

1 | INTRODUCTION

Periodontal maintenance (PM) is characterized as a programme of regular visits with selective procedures aiming to maintain periodontal health upon completion of active periodontal treatment (APT) (AAP, 2001; Chambrone & Chambrone, 2006). Based on regular maintenance care appointments individualized according to patient- and tooth-related factors (Lang & Tonetti, 2003), PM aims to prevent periodontitis progression and minimize tooth loss (Chambrone et al., 2010; Chambrone & Chambrone, 2006; Fardal et al., 2004; Goldman et al., 1986; Hirschfeld & Wasserman, 1978; Lindhe & Nyman, 1984; McFall, 1982; Tonetti et al., 1998, 2000; Wood et al., 1989). This periodic clinical regimen comprises thorough anamnesis, periodontal reassessment, radiographic review, rigorous plaque control, scaling and root planing if necessary, and polishing of teeth (AAP, 1998, 2001). Nevertheless, individual and adequate oral hygiene instructions (OHI) to the patient's needs should also be provided as it plays an important role in achieving gingival health (Tonetti et al., 2015).

Periodontal treatment is clinically effective (Renvert & Persson, 2016; Slots, 2017; Trombelli et al., 2015) and restores the levels of oral health-related quality of life (Botelho et al., 2020). However, the effectiveness of PM in preventing disease progression and tooth loss may be influenced by different factors and conditions, such as smoking, diabetes and others patient-related factors (e.g. age and gender) (Albuquerque et al., 2018; Bäumer et al., 2011; Chambrone et al., 2010; Dannewitz et al., 2016; Díaz-Faes et al., 2016; Goh et al., 2017; Pretzl et al., 2018). Also, compliance with regular PM has been associated with less risk of tooth loss (Eickholz et al., 2008; Kim et al., 2014; Needleman et al., 2018).

In 2010, a systematic review (SR) following patients for at least 5 years concluded that age, smoking and initial tooth prognosis were linked with tooth loss in the course of PM (Chambrone et al., 2010). A recent review has shown a number of important factors that may be significant predictors for tooth loss in periodontitis patients (Helal et al., 2019), however, a minimum of 3 year follow-up was considered, opposing the established minimum and required period of 5 years to be considered a long-term monitoring (Chambrone et al., 2018; Palmer & Cortellini, 2008). Therefore, this SR aimed to update the previous version of this review (Chambrone et al., 2010) by revisiting potential predictors of tooth loss among patients who underwent APT and long-term PM, by answering the following question: 'What local and systemic risk factors are associated with tooth loss during long-term periodontal maintenance?'.

2 | METHODS

This SR was developed a priori and performed according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2019) and the PRISMA guidelines (Appendix S1) (Liberati et al., 2009). Detailed descriptions of the protocol of this SR have been published previously (Chambrone et al., 2010). The following sections present a concise depiction of the general specific methodologic aspects of the 2020 version of the review.

2.1 | Criteria for considering studies for this review

Longitudinal prospective and retrospective studies (i.e. cohort, case-control and case series studies), restricted to patients with periodontitis who underwent APT and attended a regular maintenance care programme for at least 5 years (Chambrone et al., 2018; Palmer & Cortellini, 2008) were considered eligible for inclusion in this systematic review. Four criteria were considered to further evaluation of the study, as described in the previous systematic review regarding this subject (Chambrone et al., 2010): (1) data on tooth loss (i.e. number, percentage or mean number of teeth loss during PM); (2) statistical analysis performed to investigate the association between different independent variables (e.g. age, gender, smoking) with tooth loss, or at least the raw data from these variables; (3) absence of patients with a history of refractory periodontitis or AIDS; and (4) absence of patients who did not return to PM. Only studies fulfilling the latter criteria were included. The outcome measure of interest was tooth loss during PM.

2.2 | Information sources search and study selection

Detailed search strategies were developed for each database. MEDLINE (via PubMed), Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), Embase and Web of Science databases were searched up to and including September 2020, based on

the search strategy developed for MEDLINE: ((((periodontal maintenance) OR (supportive periodontal therapy)) OR (maintenance care)) OR (long-term maintenance)) OR (long-term effects) ((specialist periodontal practice) OR (treatment outcome))) AND (tooth loss OR tooth mortality OR periodontitis [MeSH] OR periodontitis OR periodontal disease [MeSH] OR periodontal disease). Reference lists of potentially eligible papers were screened (i.e. hand searching) in order to identify any other study not identified by electronic search, as well as the authors of included studies were contacted if necessary, for clarification of data or to obtain missing data. Information about data collection until September 2009 were reported previously (Chambrone et al., 2010). Identification of studies conducted from October 2009–19 September 2020 were performed by two reviewers (RC and JB) who independently screened titles and abstracts. Any paper classified as potentially eligible by either reviewer was ordered as a full text and independently screened by the reviewers. All disagreements were resolved through discussion with a third reviewer (LC).

2.3 | Data extraction process and risk of bias assessment

Two researchers (RC and JB) extracted independently the following data from the studies: (1) citation, publication status and year of publication; (2) location of the trial; (3) study design; (4) study methods; (5) patients characteristics (type of periodontitis, baseline age, % of males, % smokers at baseline, % of severe PPD, furcation and

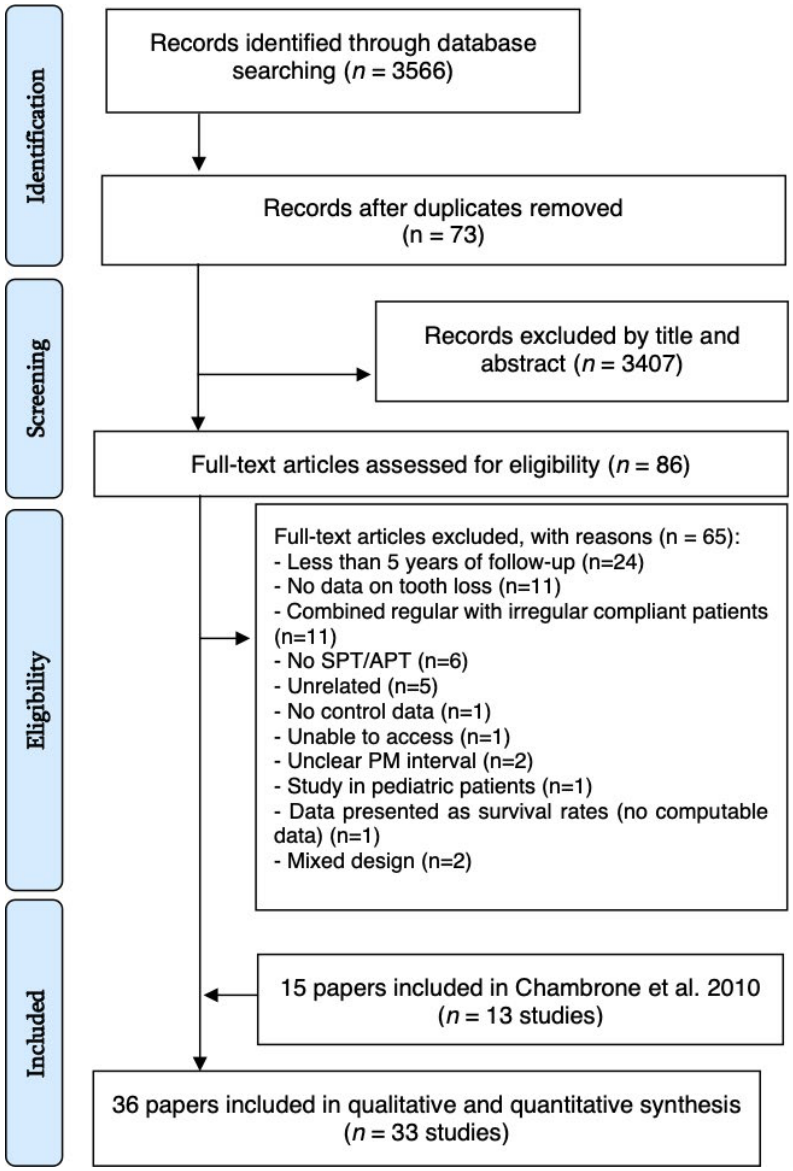

FIGURE 1 PRISMA Flow Diagram

TABLE 1 Characteristics of included studies—Prospective studies

Study	Methods	Participants	Maintenance Interventions	Outcomes	Notes	Funding
Albuquerque et al., (2018)	Prospective design, average number of SPT visits 7.1 ± 2.8, average time between SPT visits in months 6.2 ± 0.6. Observational period: 5.99 years Drop-out was 37.1% (N= 59)	39 individuals, 31 females, mean age at baseline: 48.5 ± 9.8 years, with Chronic periodontitis. Number of patients with diabetes: 10,3%. Number of smokers: 7,7%. Number of teeth present after APT 952 (mean of 24.4 ± 4.0)	Plaque control and dental hygiene instructions, coronal prophylaxis and fluoride application and mechanical non-surgical or surgical debridement, when appropriate	Total number of tooth loss during PM: 43 (4.5 ± 0.2)(0,18 tooth/patient/year). N° of teeth loss due to PR =NR. 22 Individuals did not loss any teeth.	University-based (Minas Gerais, Brazil)	NR
Preus et al., (2017)	Prospective design underwent a 3 months pre-study hygiene phase to obtain excellent oral hygiene. The use of Metronidazole (MET), absence of bacterial species with known low sensitivity to MET was required. High standard of oral hygiene during the pre-study hygiene phase, that is having less than 15% of the sites with plaque. Observational period: 5 years, SPT visits at 3, 6 and 12 months following therapy, and every 6 months after that. Drop-out was 12,5% (N= 23)	161 participants with severe chronic periodontitis, age at baseline range: 35 to 75 years. Number of patients with diabetes: NR. Number of smokers: NR. Number of teeth present after APT: 1921 (mean: 23.9 ± 4.1)	4 groups: full mouth disinfection +metronidazole (FDIS +MET), full mouth disinfection +placebo (FDIS), Scaling and root planing +Metronidazole (SRP +MET) and scaling and root planing +placebo (SRP)	Total number of teeth lost during PM: 191 (0,24 tooth/patient/year). Number of teeth lost due to PR =31. During the 5-year period, a total of 73 patients, from all groups, did not lost any teeth.	Private Practice (Oslo, Norway)	Norwegian Research Council
Costa et al., (2014)	Prospective design, Observational period of at least 5 years. Mean recall SPT visits: 11.2 ± 2.8. Time since APT 61.2 ± 3.4. Drop-out was 20% (N= 53)	96 individuals, 56 females, age at baseline range: 23–70 years, with Chronic (moderate to advanced) periodontitis. Number of patients with diabetes: 13,6%. Number of smokers: 26,1%. Number of teeth present after APT: 2274 (mean: 24.2)	Complete periodontal examination was performed and data regarding plaque index (PI), probing depth, CAL, BOP, suppuration, furcation involvement and TL were recorded.	Total number of teeth lost during PM: 57 (0,12 tooth/patient/year). Number of teeth lost due PR =46. 72 individuals did not lost any teeth	Private Practice (Belo Horizonte, Brazil)	National Council of Technological and Scientific Development

Abbreviations: AgP, aggressive periodontitis; APT, active periodontal therapy; CAL, clinical attachment loss; CP, chronic periodontitis;CS, case series; CVD, cardiovascular disease; DM, diabetes mellitus; H, healthy; NR, not reported; PM, periodontal maintenance; PPD, periodontal pocket depth; PR, periodontal reasons; RBL, radiographic bone loss; SPT, supportive periodontal therapy.

mobility at baseline, number of teeth (molars and/or non-molars) at baseline and follow-up); (6) characteristics of the interventions; and (7) Outcome measures (number of teeth lost [molars and/or non-molars; maxilla and mandible teeth]). All disagreements were resolved through discussion with a third reviewer (LC).

The risk of bias (RoB) of the included observational studies was made via the adapted version of the Newcastle–Ottawa Scale (NOS) by Chambrone et al., (2010) (see in detail in appendix S2). In this, the following points were focused: (1) Selection; (2) Comparability of patients: comparability of patients on the basis of the study design or analysis; (3) Outcome of interest (i.e. tooth loss); and (4) Statistical analysis. For each criterium, a point ('star') was assigned, except for the comparability of patients where two stars could be attributed. Studies were arbitrarily considered as being of low RoB (high methodological quality: 9–11 points), moderate RoB (medium methodological quality: 6–8 points) or high RoB (low methodological quality: <6 points), respectively.

2.4 | Data synthesis

Data were collated into evidence tables, and a descriptive summary was prepared to determine the quantity of data. The unit of measurements were standardized and converted appropriately as above mentioned. Meta-analysis estimates were pooled using DerSimonian–Laird random-effects strategy (Schwarzer et al., 2015). We used the R version 3.4.1 to calculate estimates through DerSimonian–Laird random-effects model (Schwarzer et al., 2015), as previously described (Schwarzer, 2007). All random-effects meta-analysis and forest plots were performed using 'meta' package (Schwarzer, 2007), in particular 'metabin' to compute meta-analysis of binary outcomes and 'metarate' for meta-analysis of incidence rates. Using I^2 index and Cochrane's Q statistic, we inspected statistical heterogeneity ($p < 0.1$), and chi-squared test calculated overall homogeneity (Higgins et al., 2019). All tests were two-tailed, with alpha set at 0.05. Furthermore, the weight percentage given to each study was provided in the forest plots. For dichotomous data from retrospective studies, overall graphical estimates without OR values were rendered to illustrate potential impact of location (maxillary versus mandibular) and tooth type (molars versus non-molars) on tooth loss during PM. As a continuous measure, an incidence rate meta-analysis was performed calculating, for each study, the number of tooth loss per patient divided by the mean follow-up using tooth loss per patient per year as basis of comparison, using a square root transformation approach (that is, IRS as summary measure). When studies did not provide the number of tooth loss per patient, we calculated by dividing the number of tooth loss by the number of patients. A priori sensitivity analyses (in the form of subgroup analyses) were conducted to investigate the effect of the study design (retrospective versus prospective), studies' risk of bias (low versus moderate-high) and sample size (<50 patients, 50–100 patients and >100 patients). The mean tooth loss per patient per year between the types of periodontitis was performed. Meta-regressions were performed to assess the impact on study effect sizes of moderator variables for retrospective and prospective studies. For data derived from retrospective studies, we have further detailed information following the synthesis without meta-analysis (SWiM) guideline (Campbell et al., 2020).

3 | RESULTS

3.1 | Study selection

Electronic searches retrieved 3566 titles through database searching, of which 3407 were excluded after the title/abstract manual assessment and 73 articles were duplicated (Figure 1). Of these, 65 articles did not meet the inclusion criteria and were excluded, with justifications detailed in appendix S3. Inter-examiner reliability at full-text screening was considered good (kappa score = 0.77, 95% CI: 0.69–0.85).

3.2 | Study characteristics

Thirty-six papers were included in this review (Figure 1): Fifteen case-series papers included in the previous version of this review (for details see Chambrone et al., 2010) and twenty-one (58.3% of the total) observational prospective and retrospective papers published between October 2009 and 21 September 2020 (Tables 1 and 2). Six cohorts had their data reported in more than one article (Eickholz et al., 2008; Mcleod et al., 1997, 1998; Nibali et al., 2017, 2018; Pretzl et al., 2008); thus, these papers were grouped under a single name study as follows: McLeod et al., 1997/McLeod et al., 1998; Eickholz et al., 2008/Pretzl et al., 2008; Nibali, 2017/Nibali et al., 2018. Thus, 33 studies (regarding 36 papers) were included comprising three prospective and 30 retrospective cohort studies.

Graetz et al., 2011 comprised two groups of patients (AgP and CP group), the AgP group had their data reported in another study (Graetz et al., 2017), thus, Graetz et al., 2011 data refers only to the CP group.

These studies were derived from 16 different countries, across Europe, Asia and America.

3.3 | Risk of bias assessment

The Risk of bias of the included studies was assessed using data extracted from each study (Figure 2). Twelve were considered of low RoB, twenty of moderate RoB and one of high of RoB. The Risk of Bias of the 13 studies included in the previous version of this review are described in detail in Chambrone et al., (2010). Of the 20 new studies included, none of the studies received the maximum score, 13 were of low RoB (9 scored 10 points and 3 studies scored nine points) and 8 studies were of moderate RoB (eight points) (see in detail in appendix S4). All 20 studies did the ascertainment of tooth loss by a secure record and used valid statistical analyses. The majority of studies presented adequate follow-up of patients (n = 19, 95%) and have demonstrated that the number of teeth present after active periodontal therapy was reported in the study (n = 16, 80%).

Thirteen studies (65.0%) reported adequate representativeness of patients who experienced tooth loss during PM (that is, truly or somewhat representative average sample of patients who followed regular PM), adequacy of the patients who did not experience tooth loss during PM, and twelve (60%) reported appropriate comparability of groups (patients) based on the design or analysis. Nine studies clarified teeth lost due to periodontal reasons (45%) and only three had prospective assessment of tooth loss (15%). Regarding the unit of analysis, twelve studies (60%) used teeth as the unit of analysis, and the remaining studies used the patient level.

3.4 | Synthesis of results

Overall, a total of 4381 patients treated and followed-up in a regular basis were included in these analyses.

We started by comparing estimates between retrospective and prospective studies through a subgroup analysis (Figure 3), with results showing no differences between the average tooth loss per patient per year between groups ($p = 0.444$). Thus, after confirming that retrospective studies did not impact the magnitude of the meta-analytical estimates, we decided to report both estimates as a subgroup analysis, following the GRADE approach (Schünemann et al., 2013).

We then analysed separately according to the risk of bias (low versus moderate-high risk of bias). Overall, there were no differences between the estimates of studies low risk of bias comparing to moderate to high risk of bias (have Appendix S5, $p = 0.075$).

As a number of studies presented sample sizes below 50 patients, we investigated whether this could influence final results (Appendix S6). Estimates showed no differences ($p = 0.469$) between studies with less than 50 patients (0.1 tooth loss per year per patient, 95% CI: 0.1–0.2, $p < 0.001$), 50–100 patients (0.1 tooth loss per year per patient, 95% CI: 0.1–0.2, $p < 0.001$) and with more than 100 patients (0.1 tooth loss per year per patient, 95% CI: 0.1–0.2, $p < 0.001$). All estimates presented high heterogeneity ($I^2 = 98\%$).

3.4.1 | Prospective studies

Data of the three prospective studies included in this review (Table 1) were combined into subgroup pooled estimates (Figure 3). The findings of these analyses showed that patients following regular PM had an average of 0.2 tooth loss per patient per year (95% CI: 0.1–0.3) (Figure 3), with high heterogeneity ($I^2 = 92\%$).

Meta-regression evidenced that the percentage of smokers and the percentage of diabetic patients ($p > 0.05$) did not impact on study effect sizes as moderator variables (Appendix S7).

3.4.2 | Retrospective studies

With respect to retrospective trials, the individual outcomes associated to different predictors of tooth loss in each study published since the last version of this review are described below and in Table 2, whereas the thirteen included studies from the first review are described in detail in Chambrone et al., (2010). Overall, retrospective studies presented an average of 0.1 tooth loss per patient per year (95% CI: 0.1–0.1) (Figure 3), with high heterogeneity. We have further described in detail the main conclusion in each retrospective study (Appendix S8). The raw data from patient- and tooth-related factors were available for 10 surveys and these are depicted in Figure 4a and 4b. Only five studies have reported raw data from patient-related factors, while eight describing data from tooth-related factors (i.e. site-based). Of the 33 studies included, seven did not report statistical comparisons of patient- or tooth-related risk factors (De Wet et al., 2018; Graetz et al., 2011; Hirschfeld & Wasserman, 1978; McFall, 1982; McLeod et al., 1998; Papantonopoulos, 2004; Wood et al., 1989).

Two sets of meta-analyses including only retrospective studies were performed to evaluate periodontal tooth loss during long-term PM according to tooth location (mandible versus maxilla) and tooth type (non-molars versus molars). The outcomes of pooled estimates suggested significant loss of maxillary ($p < 0.001$, $I^2 = 93\%$) (Figure 3a) and molar teeth ($p < 0.001$, $I^2 = 91\%$) (Figure 3b) compared to mandibular and non-molar teeth, respectively.

Meta-regression analyses reported no significant effect of percentage male participants, percentage of diabetic patients, percentage of smoker patients, percentage of cardiovascular disease patients and percentage of teeth with furcation lesions ($p > 0.05$) (Appendix S7).

3.5 | Periodontal treatment and PM

Regarding PM, most studies reported similar treatment protocols based on oral hygiene instructions and motivation, scaling and root planing, tooth polishing, application of fluoride gel and, if suitable, periodontal surgery. Four studies did not report the procedures performed during PM (Matthews et al., 2001; McLeod et al., 1998; Ravald & Johansson, 2012; Wood et al., 1989).

3.6 | Overall tooth loss during PM

Five studies did not report the number of teeth present after APT (Jansson & Lagervall, 2008; Matthews et al., 2001; Meyer-Bäumer et al., 2012; Papantonopoulos, 2004; Seirafi et al., 2014), two studies only reported the mean number of teeth present and loss (Jansson & Lagervall, 2008; Seirafi et al., 2014) and two did not provide the number of loss teeth during PM (Fardal et al., 2004; Jansson & Lagervall, 2008).

Regarding the remaining 27 studies, a total of 75,776 teeth of 3817 patients were present after the APT completion. During PM, 6640 teeth (8.8%) were lost. The percentages of tooth loss during PM (all reasons) varied from 1.4% (Nibali et al., 2017, 2018) to 32.7% (De Beule et al., 2017). Additionally, private practice-based studies reported an average of 0.08 tooth loss per patient per year (95%

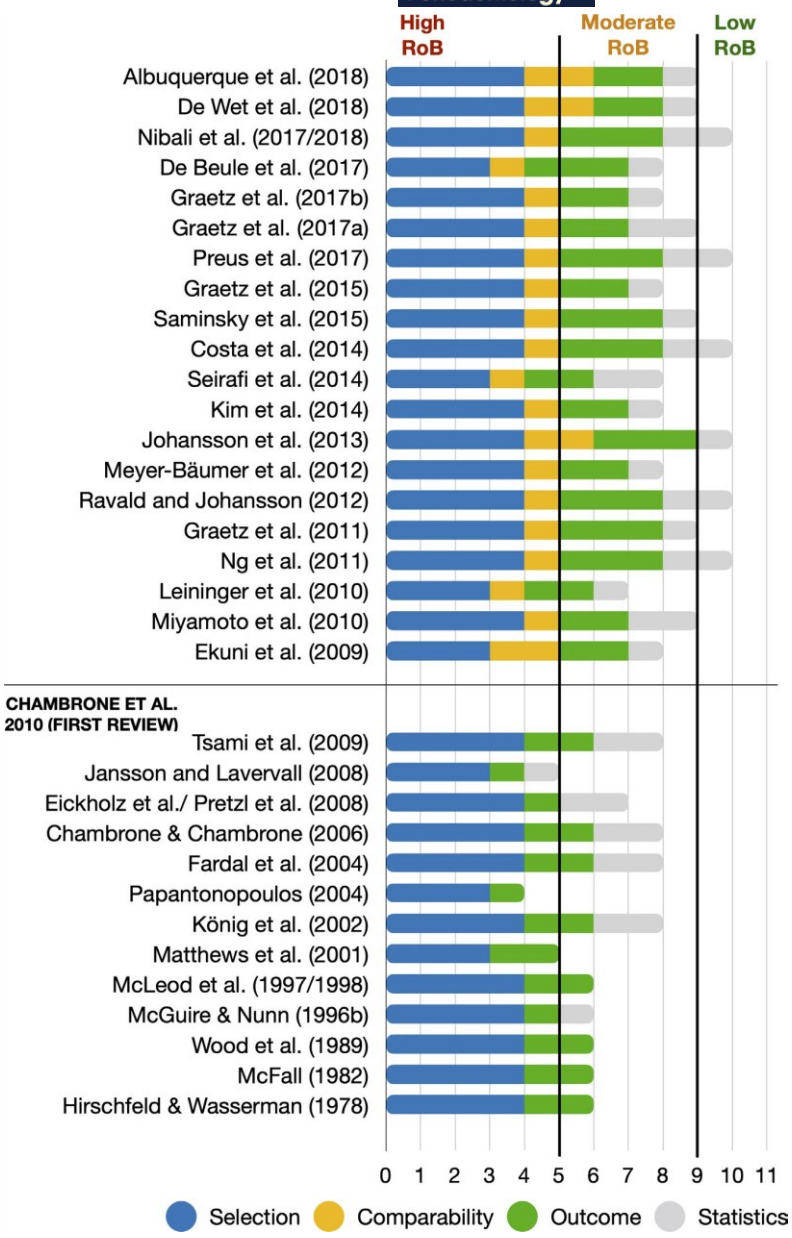

FIGURE 2 Methodological quality of included studies

CI: 0.04–0.12, $p < 0.001$), while university-based trials reported an average of 0.10 (95% CI: 0.06–0.14, $p < 0.001$), without differences between the two subgroups ($p = 0.422$) (Appendix S9).

Sixteen studies reported data on teeth lost due to periodontal reasons (PR) (Chambrone & Chambrone, 2006; Costa et al., 2014; Graetz et al., 2011; Hirschfeld & Wasserman, 1978; Johansson et al., 2013; König et al., 2002; McFall, 1982; McLeod et al., 1998; Ng et al., 2011; Nibali et al., 2017, 2018; Preus et al., 2017; Ravald & Johansson, 2012; Saminsky et al., 2015; Tsami et al., 2009; Wood et al., 1989). Concerning these studies, a total of 53,995 teeth were present after APT. During PM, 4067 teeth (7.5%) were lost, and of these 2,720 (5.04% of the teeth present after APT and 66.88% of the total number of teeth lost) due to PR. The percentage of tooth loss due to PR ranged from 0.45% (Nibali et al., 2017, 2018) to 14.4% (Johansson et al., 2013).

Regarding the comparison between the different types of periodontitis state (aggressive, chronic, undefined or overall periodontitis) there were no differences between the groups ($p = 0.527$) (Appendix S10).

3.7 | Additional analysis

Given the number of included prospective studies was below 10, publication bias was not deemed possible to carry out. Concerning

TABLE 2 Characteristics of included studies—Retrospective studies

Study	Methods	Participants
De Wet et al., (2018)	Retrospective design, observation period 10 years, mean recall interval to dental hygienist was 4.9 months, mean number of visits to periodontist was 5.3 (± 1)	54 individuals, 29 females, mean age at baseline: 48 years (± 8), with adult periodontitis. Number of patients with diabetes: 5,5%. Number of smokers: 22,22%. Number of teeth present after APT: 1358 (mean: 25.14)
Nibali et al., (2017/Nibali et al., 2018)	Retrospective design, observational period: 6,6 years, recall SPT visits between 3 to 12 months	100 participants, 60 females, mean age at baseline: 53.04 ± 9.31 years, with Chronic periodontitis. Number of patients with diabetes: 0%. Number of smokers: 22%. Number of teeth present after APT: 2449 (mean: 24.5 ± 3.8)
De Beule et al., (2017)	Retrospective design, mean observation period was 16.49 years (range 10–27), Mean SPT visits/year was 1.76 ± 0.57	402 individuals, 201 females, age at baseline 65 years (range 34 to 88), with Severe periodontitis. Number of patients with diabetes: NR. Number of smokers: NR. Number of teeth present after APT: 2434 molars (excluding third molars) (mean: 6.05)
Graetz, Sälzer, et al. (2017b)	Retrospective design, SPT visits interval of 3 to 12 months, with a observational period of 17.4 ± 4.8 years	57 participants, 35 females, mean age at baseline 34.7 ± 8.0 years, with Generalized Aggressive Periodontitis. Number of patients with diabetes: 0%. Number of smokers: 50,87%. Number of teeth present after APT: 1407 (mean: 26.5 ± 3.9)
Graetz et al. (2017a)	Retrospective design, observational period of SPT was 18.3 ± 5.7 years, SPT visits interval of 3 to 12 months	315 individuals, 179 females, mean age at baseline 48.5 ± 8.8 years (range 26–73), with Chronic periodontitis. Number of patients with diabetes: NR. Number of smokers: 9,8%. Number of teeth present after APT: 7658 (mean: 25.4 ±3.9)
Graetz et al. (2015)	Retrospective design, 2 groups: AgP and CP, observational period: 18.3 ± 5.5 years (9 to 30.8)	379 individuals, 220 females, mean age at baseline 45.7 ± 10 years, 68 individuals with AgP. Number of patients with diabetes: 2,6%. Number of smokers: 12,9%. Number of teeth after APT: 2214 molars (mean: 23.8 ± 3.9)
Saminsky et al., (2015)	Retrospective design, mean observational period: 12.7 ± 2.1 years (range 8.3–18.3)	50 individuals, 31 females, mean age at baseline: 46.6 ± 10.6 years (range 27–70), with Chronic periodontitis. Number of patients with diabetes: 0%. Number of smokers: 18%. Number of teeth present after APT: 1281 (925 non-molars) (mean: 25.6)
Seirafi et al., (2014)	Retrospective design, Observational period: 10 years; SPT visits interval of 3 to 12 months, n° of recall SPT visits: 18.69 ± 3.52	21 individuals, 17 females, mean age at baseline: 53.69 ± 11.80. Number of patients with diabetes: NR. Number of smokers: NR. Mean n° of teeth at baseline: 25.63 ± 3.46
Kim et al., (2014)	Retrospective design, mean observation period: 11.2 years (9.8–13.1), SPT visits interval of 3 to 6 months	15 individuals, mean age at baseline: 46.2 (range 34–58). Number of patients with diabetes: NR. Number of smokers: NR. Number of teeth present after APT: 344 (mean: 22.9 ± 6.4)

Maintenance Interventions	Outcomes	Notes	Funding
Dental plaque disclosed with erythrosine, selective scaling and root planing, professional teeth polishing	Total number of tooth loss during PM: 103 (66 molars, 24 premolars 3 cuspids, 10 incisors) (0,19 tooth/patient/year). N° of teeth loss due to PR: NR. 10 patients lost no teeth.	University-based (Ultrech, Amsterdam)	Regular academic appointments of Slot and Van der Weijden at the Academic Center for Dentistry Amsterdam
Medical and dental history update, clinical and (if necessary) radiographic data collection, oral hygiene re-instructions and motivation and supra and subgingival debridement	Total number of teeth lost during PM: 34 (0,05 tooth/patient/year). Number of teeth lost due to PR =11. 73 patients did not lose any teeth	Private Practice (London and Bishop's Stortford, United Kingdom)	No funding
Maintaining optimal dental plaque control, close monitoring of the evaluation of periodontal pockets with periodontal probing repeated each. SPT session, professional prophylaxis, and repeated debridement of residual lesions)	Total number of tooth loss during PM: 391 molars (0,06 tooth/patient/year). N° of teeth loss due to PR: 286.	Private Practice (Waterloo, Belgium)	NR
Re-instruction/re-motivation of patients, individual oral hygiene a professional tooth cleaning with SRP of residual pockets and polishing by a dental auxiliary	Total number of teeth lost during PM: 134 (0,14 tooth/patient/year). N° of teeth lost due to PR =NR. 19 patients did not lose any teeth. 17 patients lost more than 4 teeth.	University-based (Kiel, Germany)	University funded
Revelation of plaque followed by re-instruction and re-motivation including demonstration of tooth and interdental cleaning, professional tooth cleaning and SRP of residual pockets, followed by polishing and application of a 12500 ppm NaF gel	Total number of teeth lost during PM: 816 (0,14 tooth/patient/year). N° of teeth lost due to PR =NR.	University-based (Kiel, Germany)	University funded
Subgingival debridement with manual and power-driven instruments, and probing pocket depth and FI were re-evaluated 3–6 months after APT	Total number of teeth lost during PM: 438 molars (0,06 tooth/patient/year). N° of teeth lost due to PR =NR. 170 individuals did not lose any teeth during PM	University-based (Kiel, Germany)	University funded
Oral hygiene instructions and motivation, and scaling and root planing	Total number of teeth lost during PM: 129 teeth (0,20 tooth/patient/year). Number of teeth lost due to PR =96. 35 patients were classified as well-maintained (lost 0–3 teeth), 11 as downhill (lost 4–9 teeth), and only four as extreme downhill (lost 10 or more teeth)	Private Practice (Tel-Aviv, Israel)	No funding
All clinical measurements, oral hygiene instructions, tooth brushing (Bass method) was demonstrated in the patient's mouth while observed with a mirror, then the demonstration was repeated with dental floss and other interdental cleaners according to the patient need	Total number of teeth lost during PM: 24 (0,11 tooth/patient/year). With a mean n° of teeth in the final exam of: 24.13 ± 4.59.	University-based (Shiraz, Iran)	International Branch of Shiraz University of Medical Sciences
Nonsurgical and surgical therapy	Total number of teeth lost during PM: 23 (0,14 tooth/patient/year). N° of teeth lost due to PR =NR	University-based (Gangneung, South Korea)	NR

(Continues)

TABLE 2 (Continues)

Study	Methods	Participants
Johansson et al., (2013)	Retrospective design, mean observation period: 14.8 ± 0.7 years, SPT visits interval: 3 to 4 months	64 individuals, 35 females, mean age at final examination: 64 ± 8.7 years (range 49–91). Number of patients with diabetes: NR. Number of smokers: 31,25%. Number of teeth present after APT: 1537 (361 molars) (mean: 23.4 ± 4.8)
Meyer-Bäumer et al., (2012)	Retrospective design, 2 groups (Localized Aggressive Periodontitis (LAgP) and Generalized (GAgP), Observational period: 9.7 years (range 5–17)	LAgP: 3 individuals. GAgP: 16 individuals mean age at baseline: 30.78 ± 4.06. Number of patients with diabetes: NR. Number of smokers: NR. Number of teeth present after APT: NR
Ravald and Johansson (2012)	Retrospective design, mean observational period: 12.5 years (range 11–14)	64 individuals, 34 females, mean age at baseline: 52 ± 10.6 years (range 30–78). Number of patients with diabetes: 9%. Number of smokers: 28,1%. Number of teeth present after APT: 1537 (361 molars) (mean: 23.4 ± 4.8)
Graetz et al., (2011)	Retrospective design, mean observational period of SPT was 15.7 ± 3.6 years for CP, SPT visits interval of 3 to 12 months	34 individuals, 17 females, mean age at baseline 51.6 ± 7.4 years (range 40–69). Number of patients with diabetes: NR. Number of smokers: 11,8%. Number of teeth present after APT: 834 (mean 22.1 ± 5.2, range 9–31)
Ng et al., (2011)	2 parts: a longitudinal retrospective study and a clinical recall cross-sectional study. Observational period: 10.9 years (7.0–20.4)	239 individuals, 142 females, mean age 44.5 years (19–80). Number of patients with diabetes: 7,1%. Number of smokers: 0,42%. Number of teeth present after APT: 5891 (24.7± 4.3, range 11–32)
Leininger et al. (2010)	Retrospective design, mean observation period: 8.2 years (range 6–12). SPT visits interval of 3, 6 or 12 months depending on the initial diagnosis	15 individuals, 7 females, mean age at baseline: 51.9 years, 9 with moderate periodontitis and 6 with aggressive/severe periodontitis. Number of patients with diabetes: 3,3%. Number of smokers: 6,6%. Number of teeth present after APT: 317 (mean: 21.1)
Miyamoto et al. (2010)	A retrospective study was conducted using data from 295 patients with 20 years of observation period, which included treatment and ±15 years of maintenance therapy	98 individuals, 36 females, mean age at baseline: 43.5 years. Number of patients with diabetes: NR. Number of smokers: 22,4%. Number of teeth present at baseline: 2481 (mean: 25.3)
Ekuni et al., (2009)	Retrospective design, mean observational period 7.8 ± 2.3 years, mean number of recall SPT visits per year: 7.4 ± 3.4	25 individuals, 17 females, mean age at baseline: 52.5 ± 10.5 years, with Chronic periodontitis. Number of patients with diabetes: 0%. Number of smokers: 0%. Number of teeth present after APT: 113 (mean: 4.5 ± 2.8)

Abbreviations: AgP, aggressive periodontitis;APT, active periodontal therapy; CAL, clinical attachment loss; CP, chronic periodontitis; CS, case series; CVD, cardiovascular disease; DM, diabetes mellitus; H, healthy; NR, not reported; PM, periodontal maintenance; PPD, periodontal pocket depth; PR, periodontal reasons; RBL, radiographic bone loss; SPT, supportive periodontal therapy.

Maintenance Interventions	Outcomes	Notes	Funding
Oral hygiene instruction, supra - and subgingival scaling	Total number of teeth lost during PM: 217 (148 non-molars and 69 molars) (0,23 tooth/patient/year). N° of teeth lost due to PR =out of the 69 molars lost, 52 were lost due to PR.	University-based (Linköping, Sweden)	Research Counsil of the Public Dental Service, County of Östergötland, Sweden
GBI and PCR were assessed. The patient was re- instructed and re-motivated to an effective individual plaque control. Professional tooth cleaning followed as well as application of a fluoride gel.	Total number of teeth lost during PM: 6 (0,03 tooth/patient/year). N° of teeth lost due to PR =NR	University-based (Heidelberg, Germany)	Authors and their institutions. Tobias Hain (Hain Life-science GmbH, Nehren, Germany) provided the test kits for the Interleukin−1 composite genotype
NR	Total number of teeth lost during PM: 211 (69 molars, 3.3 teeth/patient) (0,26 tooth/patient/year). N° of teeth lost due to PR =153. 24 individuals (38%) lost no teeth, 17 patients accounted for 167 lost teeth (77%)	Private Practice (Linköping, Sweden)	Public Dental Health Care, County Council of Östergötland, Linköping, Sweden
Staining of plaque followed by re-instruction and re-motivation, utilization of interdental brushes was demonstrated and practiced by the patient in every appointment, professional tooth cleaning and mechanical subgingival debridement of residual pockets, followed by polishing using rubber cups and polishing paste with application of a fluoride gel	Total number of teeth lost during PM: 93 (0,16 tooth/patient/year). N° of teeth lost due to PR: 48.	University-based (Kiel, Germany)	University funded
Update of the medical and dental histories, re-examination of the periodontal status, debridement, polishing of teeth and application of topical fluorides	Total number of teeth lost during PM: 228 (71 single-rooted) (0,09 tooth/patient/year). Number of teeth lost due to PR =96	University-based (Singapore, Singapore)	National Dental Center Singapore and the National Medical Research Council Enabling Fund, Singapore
Periodontal examination, oral hygiene was controlled and re-inforced if necessary, residual pockets (>4 mm) were systematically scaled. Periodontal surgery was performed in case of persistence or worsening of profundo periodontal defects	Total number of teeth lost during PM: 18 (0,15 tooth/patient/year). Number of teeth lost due to PR =NR	University-based (Strasbourg, France)	University funded
update of medical history and changes of medications, periodontal examination, subgingival plaque and calculus removal using hand instruments and an ultrasonic scaler, professional mechanical tooth cleaning, supragingival plaque and calculus removal using a handpiece, fluoride varnish, reinforcement of oral hygiene	Total number of teeth lost during PM: 222 (118 non-molars and 104 molars) (0,11 tooth/patient/year). Number of teeth lost due to PR =NR	Private Practice (Yamagata, Japan)	NR
Oral examination, oral hygiene instructions, supra and sub-gingival scaling and root planing, removal of sub-gingival plaque and/or professional tooth brushing	Total number of teeth lost during PM: 37 (0,19 tooth/patient/year). N° of teeth lost due to PR =NR	University-based (Okayama, Japan)	University funded

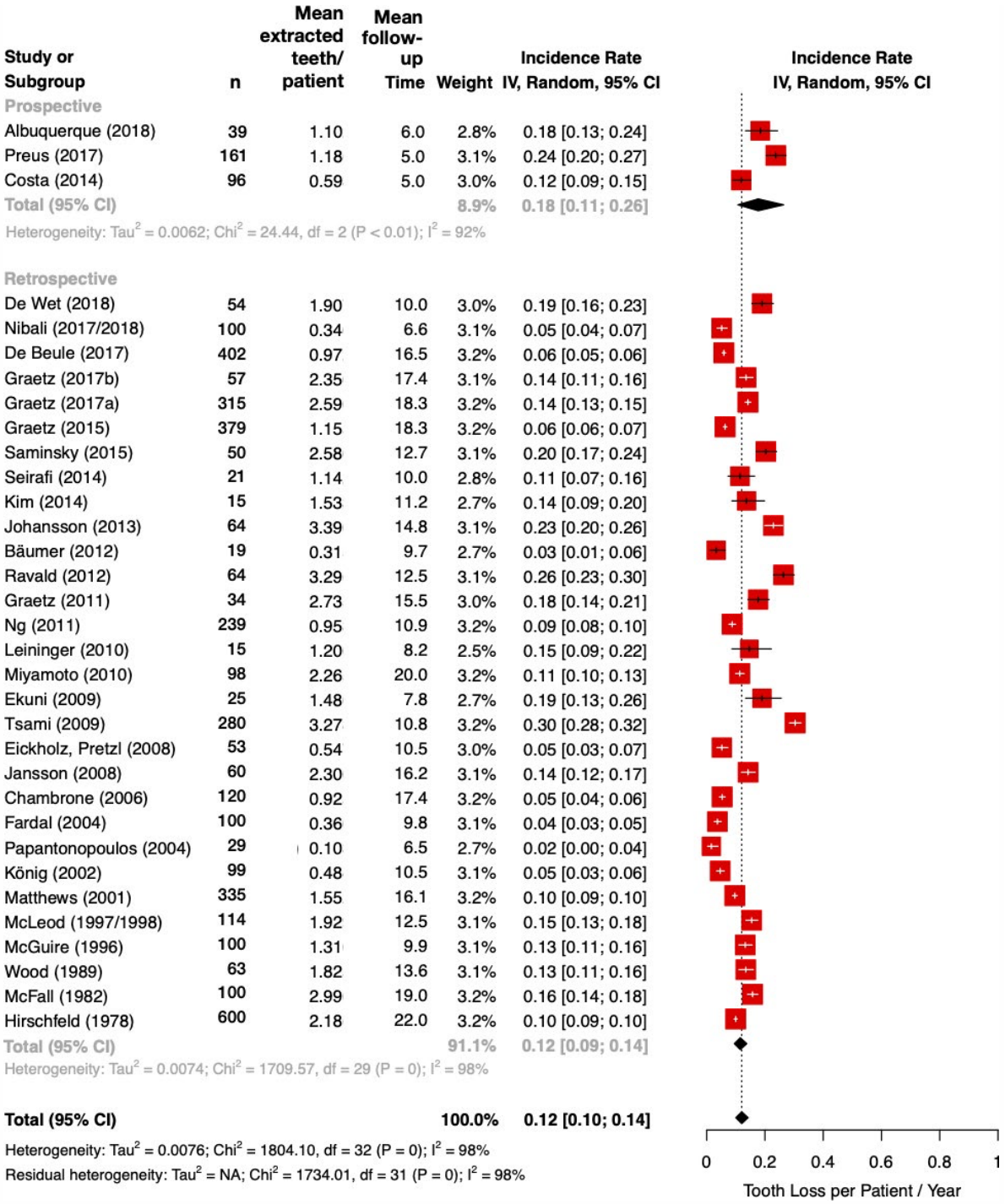

FIGURE 3 Subgroup forest plot displaying the average tooth loss per patient per year for retrospective and prospective studies

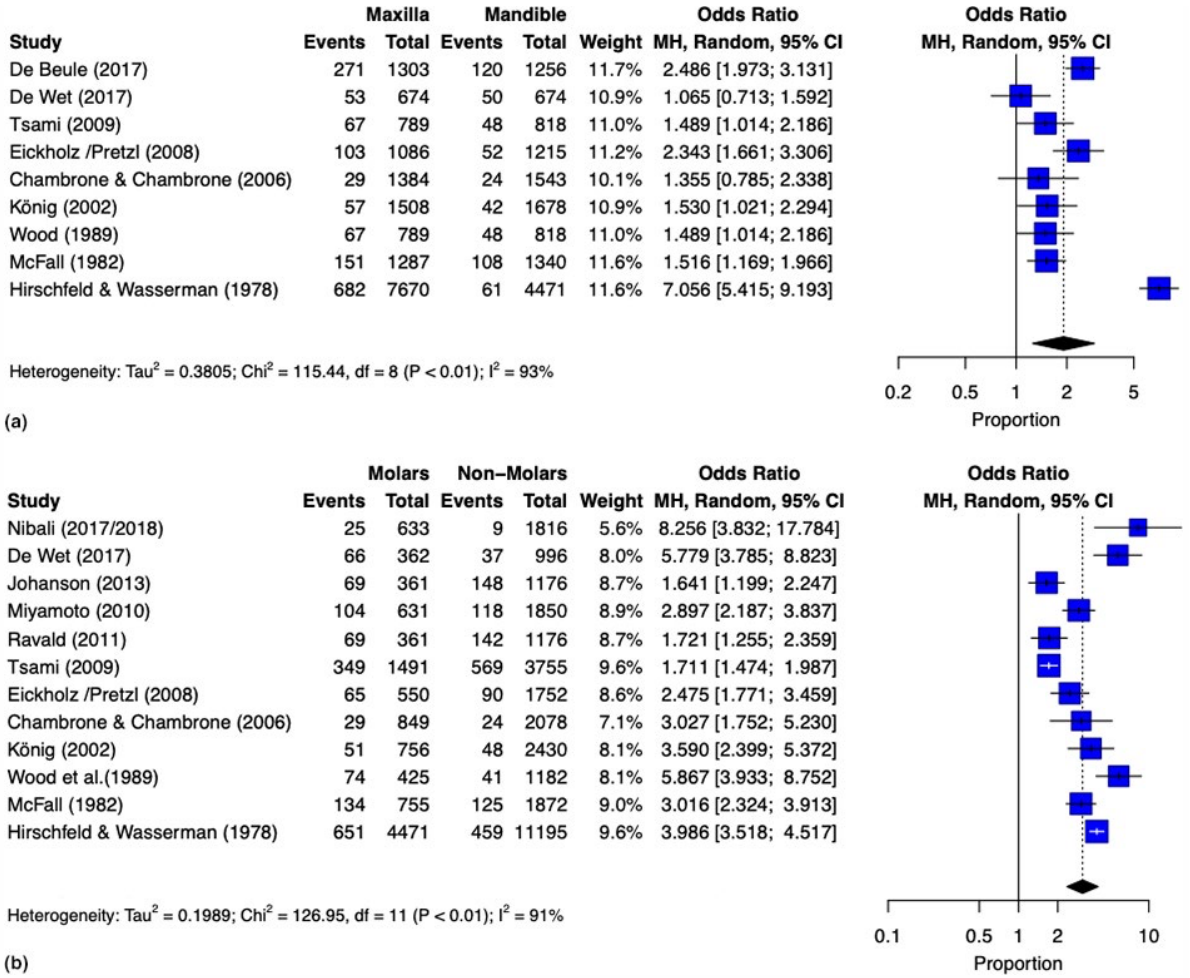

FIGURE 4 Raw data from (a) location of loss teeth and (b) type of loss teeth in retrospective studies of periodontitis

retrospective studies, results were not affected by publication bias (p = 0.3187) (Appendix S11). Considering all prospective and retrospective together, results also presented no publication bias (p = 0.2062) (Appendix S12).

4 | DISCUSSION

4.1 | Summary of the main results

This SR demonstrates that each patient in regular long-term PM might lose one tooth every ten years. As in the previous version of this review, it was confirmed by individual studies' outcomes that the majority of patient did not undergo tooth extraction due to periodontal reasons, as well as that a small number of patients was responsible for the majority of teeth lost. The number of tooth loss seems not to be dependent on the type of periodontitis.

Overall, individual studies' outcomes demonstrated patient-related factors (age, gender, active smoking and compliance regarding PM) and tooth-related factors (tooth type, tooth location, baseline PPD, presence of furcation involvement and baseline mobility) as relevant risk factors towards tooth loss during PM, however, meta-regressions revealed no significance in both retrospective and prospective trials. Graphics estimates of these studies also suggest that maxillary and molar teeth are those more prone to be lost during long-term PM. Furthermore, pooled estimates from both designs lost similar number of teeth per year per patient during long-term PM.

4.2 | Quality of the evidence and potential biases in the review process

The risk of bias appraisal evidenced an improvement in the methodological quality, since only eight studies were of moderate risk of

bias and the remaining were high quality. Thus, this development may have strengthened the validity of our results, however, the reader must bear in mind that the meta-analytical estimates were not affected by the methodological quality. Furthermore, the discussion about local and systemic factors influencing tooth loss stands as meta-regressions did not support an impact on the effect size, however, studies only report a baseline status instead of the evolution of the patient status that might have more impact potential. Regarding the impact of retrospective trials may posing important methodological shortcomings to the validity of this SR results (Chambrone et al., 2009, 2010; Needleman, 2002; Needleman et al., 2005), meta-analytical synthesis did not find any difference, however, we must be cautious on these interpretations since there are only 3 prospective studies so far and, in future updates this value must be confirmed. Therefore, we highlight that more future prospective trials are warranted.

On the one hand, it is worth highlighting some strengths of this systematic review. Contrasting with the previous work, this review could be expanded to allow the incorporation of new information (Table 3): (1) inclusion of information of 23 new studies (60.5% of the total number of included studies) and an additional number of 45,269 teeth (52.2% of the total number of available teeth) in 2845 new patients (57.0% of the total number of patients reporting the number of teeth after of APT); (2) assessment the results according to the study design (it was possible to include both individual studies outcomes and pooled estimates from prospective studies) and type of periodontitis; (3) estimation of the influence of diabetes as an additional predictor of tooth loss (i.e. pooled estimates from prospective studies could identify that both smoking and diabetes are significant factors towards tooth loss during PM); and (4) the positive effects of PM in preventing tooth loss performed in both practice-based and university-based practices. On the other hand, it is also important to take into consideration the potential limitations in the review process. It should be noted that the NOS, originally designed to assess case-control and prospective cohort studies, was adapted to evaluate the methodological quality of case series as most of the available information remains from retrospective case series. Therefore, the use of this adapted scale and the high level of heterogeneity found between retrospective and prospective studies considered eligible for inclusion, may limit the validity of the outcomes of this review, and thus the achievement of definitive conclusions. In this type of studies, patients included are highly selected and drop-out rates may be extremely high. Furthermore, the case definitions of periodontitis were very assorted precluding direct comparisons (the most adequate ones) at this time. Consequently, for retrospective studies, just display graphical estimates were displayed without an overall value to elucidate the difference of lost teeth according to the type of teeth (molar vs. non-molar), arch (maxilla vs. mandible). Hence, all the above-mentioned estimates should be taken into consideration when interpreting findings of the present review.

Additionally, it was decided to maintain a minimum follow-up period of at least 5 years of PM, even considering the high probability of excluding data from studies suitable for performing meta-analyses. However, this exclusion criteria contributes to mitigate heterogeneity and, therefore, consolidates these results. Yet, this revised work highlights, once again, the need for well-designed prospective observational studies (mainly prospective designs) that will properly assess and underpin alleged factors that contribute to tooth loss during long-term PM. Nevertheless, there is a discussion of the added value of introducing baseline variables, when what interests us is the evolution of these factors (tooth- and patient-related) over the course of PM. Another limitation may be the non-independence of molars and non-molars and teeth as the unit of analysis.

Furthermore, randomized-controlled trials (RCT) remain as high-quality studies, however, since the first revision only one RCT was published, highlighting the difficulty of attaining a follow-up of 5–10 years minimum. Arguably, the establishment of RCTs in long-term periodontal treatment seems unethical and unpracticable, as the placebo aims to produce no therapeutic effect. The only possible randomized design will be the comparison of different therapeutic and PM approaches. Therefore, the tendency will be the existence of an invariable overwhelming majority of non-randomized studies in further updates.

TABLE 3 What's new—changes from the previous review

Description
• Search methods for identification of studies: Searches were updated up to September 2020. • Inclusion of 20 new studies (60.6% of the total number of included studies). • Inclusion of 37,855 new teeth (48.4% of the total number of available teeth). • Inclusion of 2281 new patients (52.1% of the total number of patients reporting the number of teeth after of APT). • Sensitivity analyses exploring the impact of retrospective data versus prospective data. • Data from three prospective studies were included into the meta-analysis. • Meta-analysis on prospective trials regarding mean tooth loss, percentage of tooth loss and diabetes impact were included. • Meta-regression to assess the influence of smoking was performed.

4.3 | Agreements and disagreements with other reviews or studies

To the best of the authors` knowledge, only the original version of this review (Chambrone et al., 2010) and a subsequent one (Helal et al., 2019) addressed the predictors of tooth loss during long-term PM. The primary differences between the paper by Helal et al., (2019) and the present review relate to: (a) The minimum follow-up period used to establish a study as of long-term (3 years versus 5 years); (b) the number of studies (20 versus 33), patients (15,422 versus 4428) and teeth present after APT (53,433 versus 79,259) available for analysis; (c) assessment of overall tooth

loss (reasons not specified) versus the assessment of teeth lost only due periodontal reasons; (d) combination of both retrospective and prospective studies in pooled estimates versus analyses separated by study design (to improve the degree of precision and reduce the degree of heterogeneity associated to individual studies` characteristics). Moreover, it is important to highlight that one study (Cunha-Cruz et al. 2008), not included in the present systematic review, provided data of the majority of patients (81.9%, n = 12,631) evaluated in that paper by Helal et al. (2019). The Cunha-Cruz et al. (2008) paper evaluated the files of a cohort of patients with destructive periodontal disease (periodontal diagnosis criteria not defined in the study), and aged between 45 and 61 years. Interestingly, 81.6% (n = 5,453) of the 6681 extracted teeth did not undergo previous APT (Cunha-Cruz et al. 2008). Consequently, the above-mentioned discrepancies between the different systematic reviews should be taken into consideration when interpreting their results.

It is also important to note that the results of this study are collectively in agreement with both previous reviews, that is, long-term PM effectively produces a decreased incidence of tooth loss over PM. However, the patient's ontogenesis regarding health awareness remains poorly studied in the included trials, as patients with a positive health awareness might contribute to higher adherence to the PM schedule and to better oral hygiene attitudes. For instance, although the results of this review did not find differences between patients with rapid and slow forms of periodontitis, it should be noted that the number of studies with aggressive periodontitis is too small to allow a definitive conclusion on this subject. Therefore, it is still 'clinically' impossible to ascertain the real influence of periodontitis progression on the number of teeth lost during PM. The AAP/EFP new classification of 2018 (Tonetti et al., 2018) proposed a grade system that may be used to reach this objective, thus future studies may contribute to enlighten this point.

Regarding the estimates from retrospective data, molars and upper teeth are more prone to be lost during PM, in accordance with both previous reviews (Chambrone et al., 2010; Helal et al., 2019). The reason might be molar's anatomical and disease progression characteristics (Heitz-Mayfield, 2005; Heitz-Mayfield et al., 2002; Huynh-Ba et al., 2009). Also, despite the variability in smoking data, our results are in line with previous evidence as it was confirmed as a significant factor (Chambrone et al., 2010; Helal et al., 2019). Diabetes was also confirmed from estimates derived from prospective trials in this updated version.

Regarding the type of periodontal therapy performed, the variability is a source of great heterogeneity. As previously discussed in Chambrone et al., (2010), the results from surgical procedures performed before 1956 (Hirschfeld & Wasserman, 1978) cannot be compared with those performed in the late 1980 s (Chambrone & Chambrone, 2006) nor in the twentieth century. In addition, the setting where regular PM was provided, that is private versus university-based practices, was confirmed to result in similar efficiency in preventing tooth loss, despite the inter-study variations were also evident.

Furthermore, the notion of tooth prognosis has been evolving since the first revision. Overall, eight studies (22.2%) have addressed the prognosis (Chambrone & Chambrone, 2006; Ekuni et al., 2009, Eickholz/Pretzl et al., 2008; Graetz et al., 2011; Hirschfeld & Wasserman, 1978; Kim et al., 2014; McLeod et al., 1998; Wood et al., 1989), but in a similar fashion as the first revision the initial prognosis of the tooth remains a difficult parameter to be compared among studies. Besides, this element is falling in disuse as only three studies published since 2009 have further considered it (Ekuni et al., 2009; Graetz et al., 2011; Kim et al., 2014). It should be considered that the term 'hopeless tooth' may be considered somehow vague and imprecise, and this may explain its absence in most recent studies. For this reason, new strategies may gain importance such as composite prognosis codes based on tooth-level factors (e.g. probing depth, interproximal bone loss, tooth mobility) and patient-level factors (age, smoking status, diabetes control), for instance the periodontal risk assessment (Lang & Tonetti, 2003) or the recent nomogram using the staging and grading system (Ravidà, Troiano, et al., 2020).

5 | CONCLUSIONS

Most patients undergoing PM did not experience tooth loss. Long-term results suggest an average loss of 0.1–0.2 teeth per patient per year during APT. Also, there were relevant patient-related (age, gender, active smoking, compliance regarding PM) and tooth-related factors (tooth type, tooth location, baseline PPD, presence of furcation involvement and baseline mobility) towards tooth loss during PM.

5.1 | Implications for Practice

From a clinical point of view, the mean values of tooth loss per patient per year displayed during regular PM can be used with a twofold purpose as follows: 1) to inform and educate patients about the need / importance of attending regular maintenance care appointments following active periodontal therapy; and 2) to highlight the potential effects of providing a better understanding for the patient with a more complete view of the consequences of periodontal diseases. In addition, and although our results do not support any definitive conclusions, it seems reasonable to propose, individualized maintenance intervals (i.e. 3–6 months) should be established according the presentation and aggressiveness of the disease by stage (I, II, III and IV) and grade (A, B and C) and the patient`s systemic condition: Stage I and II periodontitis patients displaying a slow to moderate rate of progression and periodontal destruction (Grades A and B) may follow regular maintenance care appointments at a 6 month interval. However, Stage III and IV periodontitis patients, smoker, diabetic patients and patients with a rapid rate of destruction/progression (Grade C) should follow a shorter maintenance interval (3–4 months) (Pini Prato & Chambrone, 2020). Additionally, it is important to highlight that diabetic patients must be encouraged to maintain controlled glycemic status, as well as, smoking cessation

should be encouraged in active smokers. These steps mays improve tooth survival over time, although they cannot alter immediately the consequences of smoking.

5.2 | Implications for Research

Future studies (preferably of a prospective design) should focus on subgroup sample analysis according to the diagnosis of periodontitis and influence of systemic conditions (e.g. diabetes, smoking and other potentially relevant conditions) on the rate of tooth loss during regular PM. This will allow more accurate estimations and future comparisons via meta-analysis. Moreover, the use of the new 2018 classification for periodontal and peri-implant diseases (Berglundh et al., 2018) is recommendable to improve standardization of studies results. Also, clinical variables (such as, proportion of affected sites regarding probing depth, clinical attachment loss, bleeding on probing or even mobility and furcation) were poorly reported and precluded additional analysis to understand the impact of initial periodontal status.

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ETHICAL APPROVAL

None.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

R.C, J.B and L.C contributed to study conception and design and to the collection and data interpretation. P.M and J.B contributed to statistical analysis and data interpretation. R.C., J.B., V.M, J.J.M, G.A and L.C. contributed to data interpretation. All authors contributed to the manuscript draft and to critically revise the manuscript.

DATA AVAILABILITY STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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III. DISCUSSION

In the present systematic review, we aimed to identify predictors on tooth loss during long-term PM, updating the results of the original systematic review by L. Chambrone et al. (2010). Overall, each patient undergoing regular long-term PM may lose 0.1-0.2 teeth per year. Although findings point to one tooth lost every ten years, most patients did not experience dental extractions during PM. This clinical event is restricted to a particular group of treated patients, as previously confirmed in the first version of this review (L. Chambrone et al., 2010).

Foreseeing the onset and progression of periodontitis is pertinent when planning the course of PT (Helal et al., 2019). In this sense, several prediction models for these ends have been recently reviewed (Du et al., 2018), and a recent model has been validated for early tooth loss after periodontal diagnosis in the Egas Moniz Dental Clinic (Santos et al., 2021).

Concerning such predictors, patient-related factors (age, gender, active smoking, and compliance with PM regiment) and tooth-related factors (tooth type, tooth location, baseline PPD, presence of furcation involvement and baseline mobility) were considered risk factors for tooth loss by individual studies (Albuquerque et al., 2018; L. A. Chambrone & Chambrone, 2006; Costa et al., 2014; De Beule et al., 2017; De Wet et al., 2018; Eickholz et al., 2008; Ekuni et al., 2009; Fardal et al., 2004; Graetz, Sälzer, et al., 2017; Graetz et al., 2011, 2015; Graetz, Plaumann, et al., 2017; Hirschfeld & Wasserman, 1978; Jansson & Lagervall, 2008; Johansson et al., 2013; Kim et al., 2014; König et al., 2002; Leininger et al., 2010; Matthews et al., 2001; McFall, 1982; McGuire, 1991; McLeod et al., 1997; Meyer-Bäumer et al., 2012; Miyamoto et al., 2010; Ng et al., 2011; Nibali et al., 2017, 2018; Papantonopoulos, 2004; Pretzl et al., 2008; Preus et al., 2017; Ravald & Johansson, 2012; Saminsky et al., 2015; Seirafi et al., 2014; Tsami et al., 2009; Wood et al., 1989). In line with previous studies (L. Chambrone et al., 2010; Helal et al., 2019), smoking was also confirmed as a risk factor, despite the variability data found in individual studies. Diabetes was further confirmed as a risk factor for tooth loss during PM from prospective trials data in the updated version.

Interestingly, the type of periodontitis (aggressive, chronic, undefined, or overall periodontitis) did not demonstrate significance with tooth loss. However, the number of studies regarding aggressive periodontitis was too small to reach a definitive conclusion. Hence, it was not possible to determine the real influence on tooth loss during PM considering the periodontitis progression. An updated classification scheme for periodontal and peri-implant diseases and conditions was developed by a joint commission of the American Academy of Periodontology and the European Federation of Periodontology in 2018, now allowing staging and grading of periodontitis (Armitage, 1999; Caton et al., 2018; Lamont et al., 2018). We emphasize that the "aggressive periodontitis" term was abandoned in this new case definition, and this may difficult the clarification of the type of periodontitis in tooth loss. Henceforth, we foresee reframing into the new staging and grading scheme regarding future studies on tooth loss.

Also, molars were more prone to be lost during PM (L. A. Chambrone & Chambrone, 2006; De Wet et al., 2018; Johansson et al., 2013; Miyamoto et al., 2010; Nibali et al., 2017, 2018; Ravald & Johansson, 2012). These results can be explained due to anatomical and disease progression characteristics (Heitz-Mayfield, 2005; Heitz-Mayfield et al., 2002; Huynh-Ba et al., 2009). Moreover, upper teeth demonstrated a higher risk of tooth loss (De Beule et al., 2017; De Wet et al., 2018; Tsami et al., 2009; Wood et al., 1989), being in line with previous evidence (L. Chambrone et al., 2010; Helal et al., 2019).

Regarding the setting of practice, we did not find difference between private- and university-based trials, even though university-based studies reported an average of 0.10 tooth loss per patient per year (95% CI: 0.06-0.14, $p < 0.001$) comparing to 0.08 (95% CI: 0.04-0.12, $p < 0.001$) in private-based studies. These results fully comply with the first systematic review (L. Chambrone et al., 2010), where university-based studies reported higher mean of tooth loss per patient when compared to private practice (1.8 teeth per patient vs 1.4 teeth per patient, respectively).

Compliance was not evaluated in this review as the aim was to assess risk factors for tooth loss among regular periodontal patients. Nevertheless, several studies reported an increased risk for tooth loss in non-compliant patients (Eickholz et al., 2008; Helal et al., 2019; Kim et al., 2014; Needleman et al., 2018).

Moreover, most studies reported similar protocols when approaching PM visits based on oral hygiene instructions and motivation, scaling and root planing, tooth polish, application of fluoride gel and periodontal surgery, if applied. Although, this variability represents a source of heterogeneity, as the results from surgical procedures performed before 1956 (Hirschfeld & Wasserman, 1978) cannot be compared with contemporary studies.

An improvement in methodological quality was verified by the risk of bias evaluation, as only 8 studies were of moderate risk of bias and the remaining were considered as of high methodological quality. This improvement may enhance the results validity, sensitivity analyses did not demonstrate an influence by the methodological quality.

Furthermore, the analysis on local and systemic factors influencing tooth loss (through meta-regressions) did not support an impact of effect size, however, studies only reporting baseline statuses instead of the progression of the patient's status might have more research interest.

Also, only three prospective studies were found eligible for this review and may pose an important methodological weakness to the validity of this study (L. Chambrone et al., 2009, 2010; Needleman, 2002; Needleman et al., 2005), however meta-analytical synthesis did not find any significant difference between study designs. Nevertheless, we emphasize the need for more prospective trials of long-term follow-up.

On the one hand, it is important to discuss the strengths of this study. This review included twenty-three new studies, and an additional number of 45,269 teeth, which represented an increase of 52.2% from the previous study, and 2845 new patients. Additionally, sensitivity analyses exploring the impact of retrospective data versus prospective data allow to assess the results according to the study design and type of periodontitis. Meta-analysis on prospective trials regarding mean tooth loss, percentage of tooth loss and diabetes impact were included, where both smoking and diabetes were identified as significant factors towards tooth loss during long-term PM. Also, private-based, and university-based practices both demonstrate a positive effect in preventing tooth loss during PM.

On the other hand, some limitations must be outlined. The Newcastle-Ottawa Scale was initially developed to assess the risk of bias in case-control and prospective cohort studies, this scale was adapted by the previous review (L. Chambrone et al., 2010) to evaluate case series studies as most available information remains from retrospective studies. This, associated with high heterogeneity among studies, may represent a limitation for the outcomes of this study, as in these studies, the inclusion of patients is greatly selected. Furthermore, case definitions of periodontitis and PM follow-up period interval were not standardized, and direct comparisons were not allowed. Concerning retrospective studies, no overall value was expose in graphical estimates to clarify the difference of tooth loss in line to the tooth type (molar vs non-molar) and arch (maxilla vs mandible). Thereby all the estimates shall be heeded when interpreting the outcomes of this study. A 5-year minimum follow-up was maintained form the original review as it contributes to reduce heterogeneity strengthens these results considering, although, the risk of excluding data from suitable studies to perform meta-analysis.

Only one randomized-controlled trial (RCT) was published since the first review, and although RCTs remain as high-quality studies, ethical issues arise from the use of placebo aiming to produce no therapeutic effect, as future RCTs may only compare different treatment modalities. Consequently, non-randomize studies will continue to be the trend. Ultimately, eight studies approached the concept of tooth prognosis (L. A. Chambrone & Chambrone, 2006; Eickholz et al., 2008; Ekuni et al., 2009; Graetz et al., 2011; Hirschfeld & Wasserman, 1978; Kim et al., 2014; McLeod et al., 1997; Pretzl et al., 2008; Wood et al., 1989) as the initial tooth prognosis seems to be a difficult parameter to be compared between studies. Also, the term “hopeless tooth” is considered, to some extent, imprecise and has been disused in recently studies, with only three studies, since 2009, have implemented it (Ekuni et al., 2009; Graetz et al., 2011; Kim et al., 2014).

IV. CONCLUSION

Long-term PM was associated to an average loss of 0.1-0.2 tooth per patient per year. However, most patients did not experience tooth loss during PM.

Patient-related (age, gender, active smoking, compliance regarding PM and diabetes) and tooth-related factors (tooth type, tooth location, baseline PPD, presence of furcation involvement and baseline mobility) favors tooth loss during long-term PM.

V. FUTURE PRESPECTIVES

This updated systematic review provided estimates mainly from retrospective studies. Case-control studies reporting results of daily practice may be of interest as well with, at least, a prospective point of view. For this reason, well-designed prospective cohort studies are required to validate which predictors are proven risk factors for tooth loss during PM.

Also, these studies should focus on subgroup analysis according to the periodontitis diagnosis and influence of systemic conditions (e.g., diabetes, smoking and other relevant conditions) to the rate of tooth loss during regular PM. In all, these will allow more accurate evaluations and future comparisons in subsequent studies.

The 2018 periodontitis case definition (Tonetti et al., 2018) shall be employed to improve standardization within studies. Also, baseline periodontal clinical variables were poorly reported and precluded additional analysis to understand the impact of the baseline status, and this should be further explored.

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