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THE SYSTEMIC BENEFITS OF PERIODONTAL HEALTH

Guest Editors:
David Herrera and Phoebus Madianos

the systemic benefits of periodontal health

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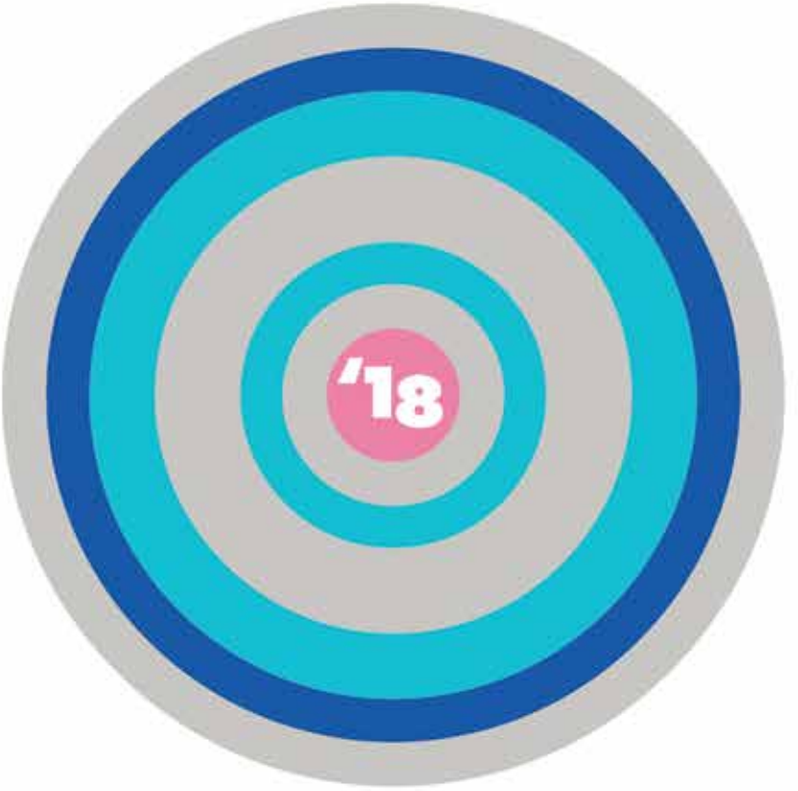

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IT'S TIME FOR ACTION.

ADRIÁN GUERRERO, PRESIDENT OF SEPA 2016-2019

SEVERAL WRITERS IN THIS MONOGRAPH have cited in their introductions the study by Kassabaum et al. (2014), a systematic review with meta-regression that includes 72 studies and which indicates that advanced periodontitis is the sixth most prevalent disease on the planet, affecting 11.2% of the global population and constituting a real problem in global public health. This problem becomes even more significant with the confirmation that patients with advanced periodontitis present a greater risk of also suffering from diabetes, cardiovascular diseases, and certain adverse pregnancy effects, among other things. In the face of these data and this evidence, dentists – especially those of us who are dedicated to periodontology – have a great social responsibility both in the prevention of periodontal diseases and in their treatment, if it is already too late for prevention. The good news is that the majority of cases of gingivitis and periodontitis can be detected and prevented in a simple way and that, with appropriate training, periodontal treatment is a procedure that is easy to carry out and accessible to the majority of the population.

The new monograph of *Periodoncia Clínica* about Periodontal Health and General Health, edited by two of the key names in international periodontology – David Herrera and Phoebus Madianos – seeks to put in the hands of the reader the refined and practical version of the existing scientific evidence on this subject. The authors have been courageous in committing themselves and providing clinical recommendations and discussing the implications about their research so that dentists can put into action the active promotion of general health within the dental practice itself.

In fact, these authors have shown us that the dentist, when treating advanced periodontitis, is reducing cardiovascular risk and is already unintentionally putting into action the primary prevention of that disease. In the same field, oral-health professionals are also in a position to use the Score code with their patients, a tool for evaluating cardiovascular risk, as indicated by the SEPA-SEC consensus document (Noguerol et al. 2016). In addition, as recommended by D'Aiuto et al. (2017), all the risk factors that are modifiable – and common to periodontitis and other non-communicable chronic diseases – such as smoking, must be tackled from the dental clinic with smoking-cessation programmes and advice on healthy lifestyle. Furthermore, Montero et al. (2017) suggest to us that, in patients with periodontitis and risk factors for diabetes, techniques of early diagnosis can be performed in the dental surgery.

Ultimately, we are not only treating teeth or millimetres of clinical attachment – we are also treating patients (Graziani et al. 2017). And, as Van Winkelhoff et al. (2017) conclude, good oral health benefits not only the teeth and the gums but also has repercussions on general health.

SEPA's commitment to science is the driver of the first step towards action. It is the result of multiple initiatives of scientific co-operation that, in recent years, have allowed us to share projects with other medical societies – especially with those of cardiology and diabetes, together with gynaecology and primary care – and which have helped us to drive the Alliance for Periodontal and General Health with the participation of many scientific, professional, and institutional entities.

Clinicians, furthermore, must be conscious that our obligation is to promote periodontal and oral health with the aim of improving the population's quality of life. Meanwhile, we must also be aware that the systemic benefits of periodontal health and the clinical implications described in this monograph help us to glimpse a new horizon in which periodontal health teams will have to involve themselves, in an active and conscious way, in the promotion of healthy lifestyle habits and, thereby, in the promotion of general health.

SEPA will thus be at the side of clinicians to make this scenario a reality, using clinical protocols endorsed by leading scientific medical societies, which will also sustain the identity of SEPA and all its members, as well as those entities that are interested in sharing and committing themselves to SEPA's main mission: the development of periodontology.

D'Aiuto F, Orlandi M. (2017) Periodontitis and cardiovascular diseases. *Periodoncia Clínica*. **8**, 51-57.

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ION ZABALEGUI, EDITOR OF PERIODONCIA CLÍNICA

THIS MONOGRAPHIC ISSUE of SEPA's *Periodoncia Clínica* about Periodontal Health and General Health provides scientific evidence focused on the relationship between periodontal health and general health, with clear indications of the implications for clinical practice.

In the light of the excellent articles contributed by some of the leading international research groups, we can claim that this evidence and association is more and more relevant and important in its everyday application in the dental practice.

Oral-health professionals must take on two obligations: one the one hand, we must be open to better understand the systemic diseases that can be affected by oral health; and, on the other hand, we must be conscious of the great opportunity represented by the possibility of carrying out primary prevention of these diseases within our surgeries.

In terms of care, the patient's presence in our clinics allows us to carry out work such as the taking of systemic data – blood pressure, blood sugar level, metabolic syndrome, etc. – and tasks of information and prevention, from a perspective of health promotion, in which the patient is placed at the centre of this process and can be provided with information and learn to adopt healthier lifestyle habits.

If the taking of blood pressure becomes a routine action in the drawing up of patients' medical histories, the amount of undiagnosed malignant hypertension among our patients will decrease in a parallel way, thus reducing vascular risk among them. I refer to this example because of cases where many patients have been grateful for this early diagnosis. It is worth giving a special mention to a case from last year: a young adult who, the day after being treated at the dental surgery and being diagnosed and informed of his condition of undiagnosed hypertension, suffered a stroke, fortunately a very mild one.

As put forward by the authors of this edition of Periodoncia Clínica centred on the systemic benefits of periodontal health, the dentist must be in a position to compile a correct medical history that reflects the connection between the periodontal and oral health of the patient and his or her general health.

Thus, to the extent that we can make use of non-invasive and innovative techniques together with simple systems of complementary diagnostic tests, oral-health professionals should collaborate closely with other colleagues from other medical disciplines and from the health sector and involve ourselves in the early diagnosis or, at the very least, in the testing of the diseases described in this monograph.

In the same way, improving and updating training about general health will be fundamental to oral-health teams. The basic knowledge of these systemic diseases, their detection, prevention, and treatment will have to be much wider if we are to encourage prevention and the well-being of patients in a more general sense, beyond oral health. The great work that is being carried out by the SEPA Foundation and the Spanish Society of Periodontology in this context must be welcomed.

I would like to express my huge gratitude for the privilege of having been able to count on David Herrera and Phoebus Madianos as guest editors of this edition, which has involved the participation of reputed experts with a proven scientific track record.

JORGE SERRANO, ASSOCIATE EDITOR OF PERIODONCIA CLÍNICA Nº 8

THE HUMAN BEING is made up of various organs and systems: locomotor, digestive, nervous, endocrine, circulatory, immune, etc. We are accustomed to seeing and studying the pathologies of each system separately. However, the human being is more than a sum of these different systems, it is a "whole" in which the different systems interconnect with and influence each other.

In our field of study, a position of good oral health means not only teeth with which to eat and smile throughout our lives, it also provides various important benefits to systemic health.

This issue reviews the current knowledge about the relationship between periodontitis and various systemic diseases, including some as important as Alzheimer's (West et al 2017), rheumatoid arthritis (Lopez Oliva et al 2017), diabetes (Montero et al 2017), cardiovascular diseases (D'Aiuto et al 2017), erectile dysfunction (Loos 2017), and various perinatal complications (Barros et al 2017). It also highlights how poor oral health can produce infections elsewhere in the body which can put people's lives at risk (Van Winkelhoff et al 2017) and how an improvement in periodontal status can produce an improvement in individuals' quality of life (Graziani et al. 2017).

It is our responsibility to inform patients of the risks implied by having poor oral health and, equally, to inform professionals in the various areas of healthcare of the multiple benefits provided by maintaining proper oral health, including a good diagnosis (as early as possible), a correct treatment of pathologies that can be observed, and – ideally – appropriate primary prevention. We should also take advantage of the dental practice to carry out an initial screening for various systemic pathologies, evaluating their risk with appropriately validated tools, and contributing to their primary and secondary prevention. It is evident that the dental practice should concern itself not only with oral health but also with the overall health of the individual. And the data provided in this issue of the magazine *Periodoncia Clínica* endorse this in a conclusive way.

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extraoral infections

extra-
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EXTRAORAL INFECTIONS BY ORAL PATHOGENS.

ARIE JAN VAN WINKELHOFF, FRANK ABBAS, THÉKE SIEBERS.

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ABSTRACT

DENTAL FOCAL INFECTIONS (DFI) are extraoral infections caused by oral pathogens. Pathological oral conditions such as endodontal and periodontal infections can cause bacteremia. Bacteremia also occurs daily by tooth brushing and other oral hygiene habits but also during dental procedures including extraction, scaling and root planing, periodontal surgical procedures and endodontic treatment. Dissemination of oral pathogens to non-oral sites can subsequently cause infections in non-oral organs and tissues. In this contribution we evaluate current knowledge on dental focal infection and summarize the most frequently occurring extraoral infections including abscesses of dental origin. We also discuss risk factors for DFI and we provide dental clinicians with some practical guidelines and recommendations. Patient care would benefit from a better collaboration between dental and medical professionals.

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INTRODUCTION

IN EGYPT, 3,500 YEARS AGO, physicians already knew that tooth infections need careful treatment because they can lead to life-threatening complications. Since then, dental focal infections (DFI), a condition that was first described by Miller in 1891, are now recognized and published in medical literature. There is ample evidence for the association between oral diseases, in particular periodontitis, and systemic disorders such as diabetes, cardiovascular diseases, stroke, respiratory infections, low birth weight and rheumatoid arthritis. This new area in medicine and dentistry is referred to as periodontal medicine and also includes extraoral infections caused by oral microorganisms. In the last three decades evidence has become available to show that the oral microbiota can be involved in all kinds of non-oral infections.

The oral microbiota

The oral cavity is the habitat of a large number of micro-organisms. In one gramme of dental plaque the number of bacteria exceeds the total number of seconds that a 75-year old human being lives. Most of these bacteria are part of the normal commensal human oral microbiome. All known types of bacteria can be found in the mouth including gram-positive and gram-negative aerobic, facultative anaerobic and strict anaerobic bacteria. The mouth is an open system, i.e. bacteria can leave and enter the oral cavity and the oral microbiota is dynamic to some extent. Bacteria that are permanently present in the oral microbiota are referred to as residents, species that are temporarily present are called transient micro-organisms. The composition of the human oral microbiome is determined by, among other factors, genetic traits, dietary, general health, behavioural and geographical factors.

The normal commensal oral microbiota forms a natural barrier for the invasion of foreign bacteria that may cause damage to the host. This natural barrier is called colonization resistance and is part of the (oral) defence system. When the natural balance between host resistance and microbiota is disturbed, disease may develop as is the case with caries and periodontal pathology. Commensal oral bacteria in general have low to moderate pathogenic potential but when numbers of bacteria exceed the maximum infectious dose they may become pathogenic. When oral bacteria become invasive they can spread per continuitatum and colonize healthy tissue. This may result in inflammation and abscess formation. Oral bacteria can also translocate to non-oral sites and may cause acute or chronic infections, which in some situations can cause life-threatening diseases such as endocarditis and brain abscesses. Abscesses are diagnosed and treated daily in hospitals. When it is not possible to incise and drain an abscess, antibiotic therapy is initiated immediately and therefore microbiological diagnosis is not always performed. As testing for strict anaerobic bacteria is often omitted, the true prevalence of dental focal infections is not known.

Translocation

Translocation of pathogenic micro-organisms from the oral cavity to other body sites frequently occurs and has been relatively well documented. Dental caries, pulpitis, periodontal diseases, odontogenic abscesses, pericoronitis and mucositis are disease conditions that allow oral bacteria to enter the submucosal connective tissue and bloodstream. Subsequently, spread occurs via the blood circulation and possibly the lymph system. In bacteremia, the blood is contaminated with microorganisms without clinical symptoms of inflammation. Bacteremia can occur after tooth-brushing, oral-hygiene procedures such as dental flossing, periodontal treatment, certain orthodontic procedures, extraction and various oral surgical procedures (Kinane et al. 2005). Aspiration of oropharyngeal secretions, saliva, dental plaque and pus from suppurating periodontal/peri-implant pockets can introduce oral bacteria to the lower respiratory tract and cause pulmonary infection, i.e. aspiration pneumonia (Scannapieco & Cantos 2016). Translocation of oral bacteria by saliva to body sites other than the lungs has been suggested but there is limited evidence for this way of transmission.

Risks of oral bacteremia

Bacteremia in immunocompetent patients is most often without signs of disease because healthy individuals are able to rapidly clear the bacteria from the blood. However, elevated temperature and other signs of disease may occur in a small proportion of healthy individuals after oral bacteremia (Siminoski 1993). The induction of systemic symptoms is probably related to the load of bacteria released into the blood circulation. A bacteremia is an early form of an infection that may progress to a sepsis, which is a life-threatening host response to infection leading to (multiple) organ dysfunction and eventually septic shock and death. Sepsis has a high mortality rate and the early administration of adequate antibiotics are an essential part of the treatment.

Sepsis from oral abscesses has been described with lethal outcome (Carter et al. 1992). Patients with an underlying cardiac condition, patients with a history of endocarditis and also patients with prosthetic devices/ prosthetic material or other sites with a *locus minors resistentiae* may run an increased risk for infection caused by oral bacteremia. For instance, periprosthetic joint infection is the most common infectious complication after total knee arthroplasty (Zmistowski et al. 2013). This infection might be caused by haematogenous bacterial dissemination and oral pathogens may be involved in these late infectious complications (Zimmerli et al. 2004).

It is hypothesized that patients with a cyanotic congenital heart or a right-to-left intracardiac shunt or with a patent foramen oval (PFO) may constitute a risk for intracranial infection such as the brain abscess caused by oral pathogens (Kagawa et al. 1983, Kawamata et al. 2001). A PFO allows oral bacteria to bypass the pulmonary circulation and cause a brain abscess (Hasan et al. 1997). Poor oral health, in combination with alcohol or/and drug abuse, is often mentioned as risk factors for DFI.

Evidence of oral dissemination

In order to establish the oral cavity as the origin of detected extraoral infections, the species must be isolated from the mouth and the infection. Definitive proof is based on analysis of the bacterial DNA of the bacteria isolated from both sites. Strong indication can also be obtained when bacterial species are found in extraoral infections that have a known and unique oral ecological niche. For instance, *Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans* are strict oral species and isolation of one of these species from an extraoral infection can be attributed to oral dissemination with great certainty. Oral bacterial species frequently found in extraoral infection involve streptococci (non-haemolytic streptococci, *S. intermedius*), gram-negative anaerobes (*Fusobacterium* spp., *Prevotella* spp.), gram-positive anaerobes (*Actinomyces* spp., *Parvimonas micra*, *Eubacterium* spp.) and facultative anaerobic species (*A. actinomycetemcomitans, Eikenella corrodens, Capnocytophaga* spp.).

Eye infections

Several cases of endogenous endophthalmitis have been described after dental procedures, involving oral bacteria such as *Streptococcus intermedius* (May et al. 1978) and group G streptococci, (Ziakas et al. 2004). *A. actinomycetemcomitans* has been implicated in several cases of endogenous endophthalmitis. Van Winkelhoff et al. (1991) described a case (see Case 1, Figures 1 and 2) of anaerobic conjunctivitis caused by three periodontal pathogens and suggested that translocation by saliva may have taken place. Several ophthalmologists had treated the conjunctivitis with medications based on the expected aerobic origin. None of these treatments resulted in a cure. Dental as well as medical professionals are usually not aware of oral pathogens as a cause of conjunctivitis.

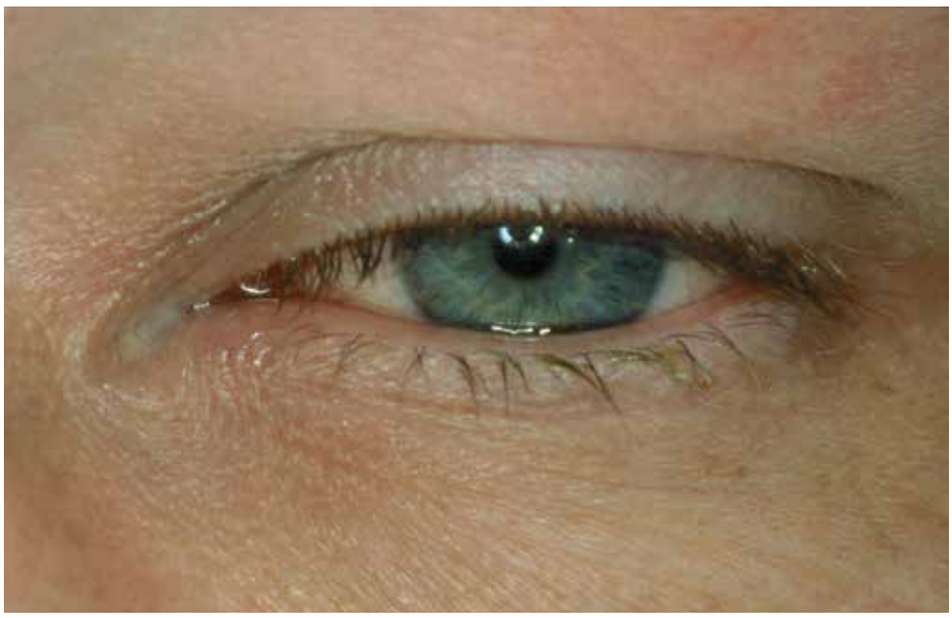

Figure 1.
The patient's left eye with purulent discharge.

CASE 1. A 33-year old male patient was referred to a periodontal clinic for severe periodontitis. Aggressive "purulent" periodontitis was diagnosed. Upon examination the periodontist (FA) also noted a purulent discharge from the left eye (dacryopyorrhea) (Figure 1). Several ophthalmologists had diagnosed and treated for conjunctivitis (Figure 2) with multiple medications based on the more common aerobic origin. None of the treatments had resulted in a cure. Microbiological analyses of subgingival samples as well as from the conjunctival sac revealed strict anaerobic bacterial species including *Prevotella intermedia and Parvimonas micra*, two species that were also isolated form the periodontal pockets and the dorsum of the tongue. Restriction Enzyme Analysis of the *P. intermedia* isolates from the mouth and the eye showed high similarity, indicative for transmission of the oral *P. intermedia* to the eye. Treatment with systemic metronidazole and amoxicillin resulted in a rapid and complete cure of the eye infection. Control testing after 4 months revealed no residual pathogens (van Winkelhoff et al. 1991).

Cardiovascular infections

The offending organisms in infective endocarditis are frequently oral bacterial species such as *Streptococcus* spp. Gram-negative endocarditis can also be caused by oral bacteria of the HACEK group and these are involved in 1-3 % of the cases (Revest et al. 2016). The HACEK group is a collective of facultative anaerobic oral gram-negative oral bacterial species and includes *Haemophilus spp*., *A. actinomycetemcomitans, Cardiobacterium hominis, E. corrodens and Kingella kingae*. This type of endocarditis has a good prognosis and simple management if correctly identified. Delay in microbial diagnosis can however result in fatal infection (Sharara et al. 2016). Most cases of *A. actinomycetemcomitans*-associated endocarditis show no vegetations and the characteristic peripheral stigmata (petechiae) of endocarditis are often not observed (Chen et al. 1991). Endocarditis in patients with prosthetic heart valves has been described in many case reports and *A. actinomycetemcomitans* has been implicated in this condition (Van Winkelhoff & Slots, 1999).

Figure 2.
Conjunctivitis of the left eye.

A consequence of *A. actinomycetemcomitans* endocarditis might be formation of emboli and this might result in ocular, cerebral, coronary or pulmonary complications. Binder et al. (2003) reviewed 5 cases of *A. actinomycetemcomitans* endophthalmitis and noted that 4 of the cases suffered from pre-existing heart abnormalities, endocarditis was present in 3 patients. The authors note that endocarditis should be ruled out in every patient with *A. actinomycetemcomitans* endophthalmitis and they recommend thorough dental examination in each patient and periodontal disease should promptly be treated. Infective endocarditis is a serious disease and associated a range of (severe) complications. Infective endocarditis, for instance, can lead to congestive heart failure or may extend into the valve annulus and cause paravalvular abscess and fistulas. These conditions need immediate surgical treatment. David et al. (2007) found that paravalvular abscess is associated with *Streptococcus viridans* in 26% of native valve infections and in 7% of prosthetic valves cases.

Extraoral abscesses and oral pathogens

Dissemination of oral pathogens can result in empyema (formation of pus in an existing space such as sinus, pleural, subdural space), in abscess formation (formation of pus in a non-existing space) or in epithelial or endothelial infection. Infection or abscess formation in tissues and structures adjacent to the oral cavity can occur and may include submental space infection, Ludwig's angina, facial-space infections, necrotizing fasciitis, osteomyelitis of the jaw, acute maxillary sinusitis, peritonsillar abscess formation, suppurative arthritis of the temporomandibular joint, and orbital cellulitis and abscess formation (Olson & Van Winkelhoff 2015). Non-oral infections and abscesses associated with oral bacteria have been described in many tissues and organs including brain, eye, lung, mediastinum, heart, skin, soft tissues, bone and joints (Van Winkelhoff & Slots 1999).

Intracranial abscesses

Brain abscesses are serious and potentially lethal infections. The incidence is estimated to be between 1-8/100,000 subjects per year (Moazzam et al. 2015). The infection can be caused by bacteremia after dental treatment (Li et al. 1999). Often the oral cavity is not part of the initial medical examination and not considered as a potential primary focus of infection. Basyuni et al. (2015) described a patient with a thalamic abscess secondary to severe periodontal disease as a serious oral infection. Despite total extraction and repeated abscess drainage the patient did not survive.

Figure 3.
CT scan of the brain showing three separate lesions.

A recent systemic review revealed that 41% of the cases had experienced dental treatment within 18 days before clinical manifestation of the brain abscess. In a significant number of these cases (86.7%) 'intraoral pathology' was present with the highest prevalence for caries (35%) and periodontitis (43%) (Moazzam et al. 2015). These authors also studied the laterality of intraoral and intracranial infections and found that 70% of cases reported intracranial pathology to be on the same site as underlying intra-oral pathology. It has been suggested that a patent foramen oval (PFO) in a patient with periodontitis may be a risk factor for the development of a brain abscess caused by oral pathogens (Kawamata et al. 2001).

Figure 4.
An orthopantogram of the dentition of the patient.

Figure 5.
Photograph of the mouth of the patient showing multiple Candida lesions reflecting the immunocompromised status of the patient.

In several cases a brain abscess was initially diagnosed as a cerebral metastasis of a suggested lung carcinoma (Kuijper et al. 1992, Rahamat et al. 2011). When oral pathogens are involved in a brain abscess, multiple anaerobic pathogens are usually detected, such as *P. micra, Fusobacterium nucleatum* and *Prevotella spp. A. actinomycetemcomitans* has also been found (Moazzam et al. 2015, Rahamat et al. 2011). It has been suggested that maxillary and mandibular foci have an equal incidence in relation to intracranial abscess formation and that diseased molar teeth are most frequently associated with brain abscesses (Moazzam et al. 2015).

Rahamat-Langendoen et al. (2011) described a typical case of a patient with a brain abscess (see Case 2, Figures 3, 4 and 5). It has been noted that poor dental condition can be a risk factor for brain abscesses caused by oral pathogens and that symptoms may point towards a neoplasm rather than an infectious lesion, as it was in the case described here.

CASE 2. A 42-year old man was admitted to the hospital with a history of confusion and reduced consciousness. The patient was a heavy smoker and suffered from alcohol abuse. Several laboratory parameters were elevated such as the C-reactive protein (CRP) (34 mg/L). The computed tomography of the patient's brain revealed multiple intracerebral lesions, which were primarily diagnosed as brain metastases of an unidentified tumour (Figure 3). Upon biopsying, the lesions appeared to be abscessed. Molecular diagnostic testing showed presence of *A. actinomycetemcomitans* in the pus of the brain lesions. The patient's poor dentition was affected by caries and severe periodontitis (Figure 4). Severe oral candidiasis was present reflecting the immunocompromised status of the patient (Figure 5). The patient was successfully treated with ceftriaxone and metronidazole (Rahamat-Langendoen et al. 2011).

PRACTICAL IMPLICATIONS

BASED ON THE EXISTING LITERATURE, the dentist should be aware of oral inflammatory processes being the source of pathological conditions elsewhere in the human body either by dissemination of oral bacteria via the bloodstream or by saliva. Careful medical anamnesis and clinical examination are active steps that may connect oral conditions, in particular periodontitis, with non-oral diseases. Case 2 illustrates this approach. Likewise the importance of good oral healthcare needs to be stimulated. Maintaining oral health not only benefits the dentition but also general health. On intensive care units, chlorhexidine mouthwash or gel is used to decrease the risk of developing ventilator-associated pneumonia in critically ill patients (Hua et al. 2016). In addition, pre-operative application of chlorhexidine gel may reduce dental post-operative complications (Torres-Lagares et al. 2006, Haraji et al. 2014).

Dental procedures might release gross amounts of oral pathogens producing bacteraemia or even sepsis. Detailed knowledge of guidelines on antibiotic prophylaxis is necessary to make appropriate decisions about the administration of antibiotics. Accessible consultation between the dentist and medical clinician is important to optimize prophylaxis for the individual patient. Furthermore, it is the duty of the dentist to provide adequate information to the patient. If a patient is reluctant to maintain a proper oral health the dentist should inform the patient about the interaction between oral and possible general pathology.

Due to the incubation period, the link between the oral conditions and remote inflammation is not always recognized, especially in brain abscess conditions. This link can also be missed due to inappropriate sample collection or suboptimal transport of a specimen to a laboratory of medical microbiology. As oral pathogens often grow under anaerobic circumstances the protection from deleterious effects of oxygen is necessary. These pathogens require optimized growth conditions and often prolonged incubation of the media is necessary. Therefore not only the dentist should be aware of extraoral manifestations of oral pathology but also general medical practitioners and specialists need to know about the possibility of remote oral pathology. It is mandatory for both professions to work together and be aware of the interaction between the oral cavity and the rest of the human body. This will benefit the overall patient care.

Traditionally oral pathogens were considered susceptible to the commonly used antibiotics. In recent years however, the antimicrobial resistance among anaerobes is increasing globally (Schuetz 2014). There are indications that clindamycin resistance is widespread among anaerobic bacteria in several European countries (Veloo et al. 2015). Also, metronidazole-resistant strains have been described recently (Alauzet 2010, Veloo et al. 2012, Veloo & Van Winkelhoff 2015). Not only will this have implications for the treatment of dental infections but also for extraoral infections. As antimicrobial susceptibility testing for anaerobes is usually not performed, incorrect treatment of life-threatening extraoral manifestations might occur.

CONCLUSION

MAINTAINING GOOD ORAL HEALTH not only benefits the dentition but also general health. As extra-oral infections might cause life-threatening diseases, this is of major importance. The dentist needs to perform a careful medical anamnesis and clinical examination in order to connect oral pathology with non-oral diseases. Detailed knowledge of guidelines on antibiotic prophylaxis is necessary to make decisions about appropriate antibiotic administration. In addition medical professionals need to be aware of extraoral manifestations of underlying oral diseases. This is of particular importance as examinations often fail to identify predisposing factors of extraoral abscesses. To optimize the patient care both professions need to be aware of the interaction between oral and extraoral pathology.

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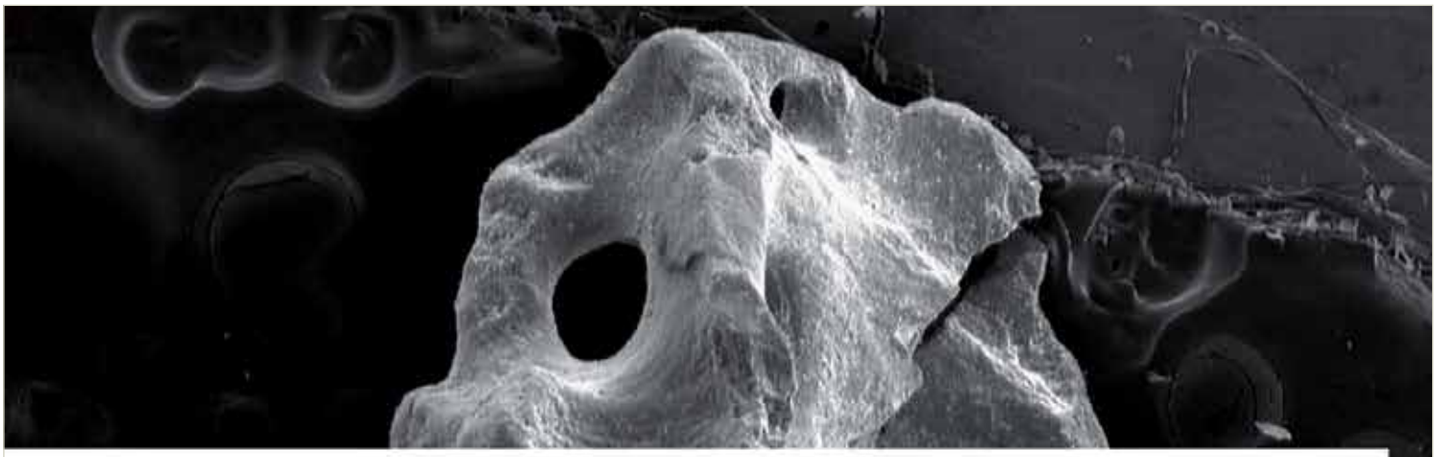

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THE ROLE OF MATERNAL PERIODONTAL DISEASE IN PERINATAL COMPLICATIONS.

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ABSTRACT

ADVERSE PREGNANCY OUTCOMES ARE FUNDAMENTAL public-health problems and many studies indicate that periodontal infections might cause adverse pregnancy outcomes. Evidence of an association between periodontal diseases and increased risk of preterm birth and low birth weight has been shown. Recently, some reports indicated that oxidative stress during pregnancy may play a role in adverse outcomes among mothers with periodontitis. The influence of periodontal infection on pre-eclampsia, which is one of the adverse pregnant outcomes, has also been reported. In this review article, we will discuss the evidence supporting the risk of adverse pregnancy outcomes in periodontitis patients and the potential effect of periodontal treatment on pregnancy outcomes, and propose adequate dental care to maintain periodontal and systemic health in pregnant women.

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INTRODUCTION

PRETERM BIRTH (<37 weeks gestation) and low birth weight (<2500 g) are fundamental public-health problems. Approximately 1 million babies die from prematurity every year and many survivors are disabled (Chang et al. 2013). Worldwide, 15 million babies are born pre term with two decades of increasing rates in almost all countries. In Europe, preterm birth rates also rose in most countries (Zeitlin et al. 2013). Rises in the multiple birth rate as well as in the preterm birth rate for multiple births contributed to increases in the overall preterm birth rate.

Pregnancy complications are multi-factorial, and many studies suggest that periodontal diseases can effectively contribute to the infectious and inflammatory stimuli associated with the cascade of events leading to increased prevalence of adverse pregnancy outcomes. A systematic review showed that there is evidence of an association between periodontal diseases and increased risk of preterm birth and low birth weight, especially in economically disadvantaged populations (Xiong et al. 2006). An extensive body of literature supports the concept involving the association of maternal periodontitis and adverse pregnancy outcomes, independently of traditional risk factors related to pregnancy complications (Ide & Papapanou 2013). However, studies had a high degree of heterogeneity and the underlying mechanisms have not been clarified. In this article, we review the relationship between periodontal infection and adverse pregnancy outcomes and summarize the current concepts regarding the biological plausibility of perinatal complications.

Biological plausibility

Two possible pathways have been proposed to associate periodontal infection with birth outcomes (Madianos et al. 2013). Firstly, oral microorganisms and their components could reach the placenta and directly induce inflammation. Secondly, inflammatory mediators locally produced in periodontal tissues or other organs such as the liver circulate and indirectly influence the foetal-placental unit. Placental inflammation, in turn triggers impaired nutrient maternal-foetal nutrient exchange, diminished placental secretion of key foetal growth factors including fibroblast growth factor (FGF2) and brain-derived neurotrophic factor (BDNF) with the inflammatory component weakening placental membranes and enhancing uterine contractility.

Detection of periodontal bacteria in placenta or amnion fluid has been shown. Many kinds of major periodontal bacteria, such as *Campylobacter rectus, Tannerella forsythia, Porphyromonas gingivalis* and *Fusobacterium nucleatum*, were detected in both amniotic fluid and in subgingival plaque samples of patients who gave birth to preterm birth and/or low-birth-weight neonates (Ercan et al. 2013). As part of the human microbiome project, Aagaard et al. (2014) reported that the organisms associated with the placenta are most closely similar to those of the oral cavity with higher numbers associated with prematurity. It is widely known that periodontal bacteria enter the systemic circulation and induce bacteremia even after tooth brushing (Lockhart et al. 2008). Thus, although the total numbers of bacteria are relatively low, the placenta is not a sterile tissue and the microbes originate from the oral cavity rather than vaginally or enteric routes. Oral translocation that results in placental exposure is not an unreasonable pathway, especially when oral inflammation increases the duration of the transient bacteremia and the biodiversity of the bacterial bolus that serves as a systemic blood-borne inoculum.

Elevated systemic inflammatory reaction in pregnant women with periodontitis has been also shown. Moderate to severe periodontitis was associated with an elevated C-reactive protein (CRP) level among African-American pregnant women after adjusting for age, smoking, parity, marital status, insurance status, and weight (Horton et al. 2008). Production of prostaglandin E2 (PGE2) in increased inflammatory reaction might induce adverse pregnant outcomes (Madianos et al. 2013). Historically, an elevated sedimentation rate and an elevated CRP level has been a hallmark of risk for preterm delivery and small-for-gestational-age deliveries. The elevated sedimentation rate has been traditionally been attributable to increases in immunoglobulin (Ig) M and IgG to an antigen of unknown origin. Our data suggest that the IgG response is directed to oral organisms with a high prevalence of mothers displaying elevated titers to typical oral organisms. These findings suggest that periodontal diseases might be one possible source of the infectious/inflammatory stress that drives prematurity.

Recently, it has been suggested that oxidative stress may play a role in the relationship between periodontitis and preterm birth and/or low birth weight by 1) enhancing hepatic CRP release, 2) by modulating the vasculature of the placenta itself – inducing hypertensive traits and 3) dampening the protective IgG/IgM response that protects the placenta from exposure to exogenous pathogens. Moreover, many studies have reported the influence of periodontal infection on pre-eclampsia, which is a placental hypertensive condition of pregnancy.

Placental changes in pre-eclampsia mirror an accelerated hyperlipid deposits of oxidized lipids into the vessels of the placenta, with vascular plaque accumulation, perivascular edema, vascular hypertension attributable to vessel narrowing and even calcification. Indeed atherosclerotic changes and placental calcifications occur normally during the third trimester of gestation with histological finding increasing steadily throughout gestation. Oxidative stress and pre-eclampsia expedite these changes such that the blood flow and nutrient exchange can be compromised to the foetus in the second trimester. The foetus sensing danger can trigger the release of estrogen precursor molecules – as part of its own flight or fight mechanism – to induce labour. In other words, a stressed foetus can precipitate the onset of labour by secreting hormones that initiate and facilitate parturition. A most dramatic demonstration of this effect is in Zica-virus-induced microencephaly. The babies never go into labour – no uterine contractions and cervical dilation and therefore must be delivered by Caesarian section surgery.

Oxidative stress

Recently, researchers showed the association of periodontal infection and oxidative stress during pregnancy. Cellular reactive oxygen species (ROS) and their control by antioxidants are involved in the physiology of the female reproductive system (Al-Gubory et al. 2010). Oxidative stress has emerged as a likely promoter of several pregnancy-related disorders, such as pre-eclampsia foetal growth restriction, preterm labor and low birth weight. Nutritional and environmental factors may influence adverse pregnancy outcomes partly via impairment of the antioxidant defence systems and enhancement of ROS.

Periodontitis subjects have high levels of local and systemic biomarkers of oxidative stress (Chapple & Matthews 2007, Singer et al. 2015). Oxidative stress accompanied by excess ROS activity plays a role in periodontal tissue destruction. Many reports support peripheral blood neutrophil hyper-reactivity in periodontitis with respect to ROS generation. Hickman and colleagues found that low socioeconomic status and the presence of moderate to severe periodontitis were significantly associated with increased oxidative stress as measured by maternal serum 8-isoprostane (Hickman et al. 2011) (Figure 1). Gümüş and colleagues showed changes in the oxidant/antioxidant balance in saliva during pregnancy and after birth (Gümüş et al. 2015).

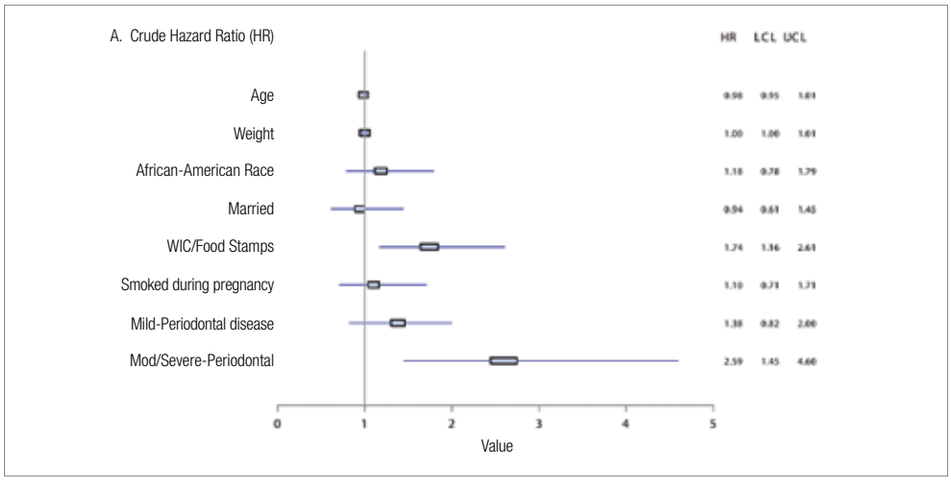

Figure 1.
Multivariable regression model for elevated serum 8-isoprostane levels (>75th percentile) (adapted from Hickman et al. 2011).

Table 1. Risk ratio and 95% confidence interval for pre-eclampsia (Ruma et al. 2008, modified).

	Non-periodontal disease	Periodontitis
CRP < 75 percentile	1.0 (referent)	3.1 (0.7-14.0)
CRP >= 75 percentile	2.3 (0.2-26.8)	5.8 (1.2-26.9)

CRP, C-reactive protein. Adjusted for gestational age at delivery and smoking history.

This evidence suggests that periodontal infection might affect pregnancy outcomes via oxidative stress. Further study is needed to determine the role of maternal oxidative stress in periodontal diseases-associated adverse pregnancy outcomes.

Pre-eclampsia

Pre-eclampsia is a pregnancy complication characterized by high blood pressure and alteration of renal functions and affects both mothers and their babies with considerable foetal mortality and morbidity (Roberts & Cooper 2001). Women with preeclampsia experience double the risk for cardiovascular disease, cardiovascular-disease-related mortality and stroke (Leslie & Briggs 2016). Many studies discovered that there was also an association between periodontal disease and pre-eclampsia (Boggess et al. 2003).

Ruma et al. showed a relationship between maternal periodontal diseases with systemic inflammation and an increased risk for pre-eclampsia (Ruma et al. 2008). In a clinical study of 775 pregnant women, the presence of periodontitis accompanied by elevated CRP level was associated with a 5.8-fold increased risk for pre-eclampsia compared to women without periodontitis and CRP elevation after adjustment for gestational age at delivery and smoking history (Table 1). Chaparro and colleagues reported, in a cohort study, that pregnant women with periodontitis, who later suffered from pre-eclampsia, showed increased levels of inflammatory markers (Chaparro et al. 2013). Elevated levels of interleukin-6 in gingival crevicular fluid and CRP in plasma during early pregnancy increased the risk of developing pre-eclampsia. Although smoking is potentially a major shared risk factor for periodontitis and pre-eclampsia, a significant relationship between periodontitis and the occurrence of pre-eclampsia was identified even among never-smokers (Ha et al. 2014). Lee et al. showed that pregnant women with both pre-pregnancy obesity and periodontitis were significantly more likely to have preterm birth with pre-eclampsia than pregnant women with only periodontitis (Lee et al. 2016). The synergistic effects of maternal obesity and periodontitis might induce preterm birth and pre-eclampsia. Recently, epigenetic alteration was observed in placenta of women with pre-eclampsia. Martin et al. revealed CpG hypomethylation as an activator of transforming growth factor beta-associated gene expression in the pre-eclamptic placenta (Martin et al. 2015). Because epigenetic modification induced by periodontal inflammation was suggested (Barros & Offenbacher 2014), pre-eclampsia might be associated with periodontal diseases via epimutation.

Wei and colleagues conducted a meta-analysis to summarize the risk of pre-eclampsia with periodontal diseases patients (Wei et al. 2013). Thirteen observational case-control studies and two cohort studies, involving more than 1,000 pre-eclampsia patients, were identified. Based on a random-effects meta-analysis, the authors found a significant association between periodontal diseases and pre-eclampsia (odds ratio = 2.79, $P<0.0001$). These results raise a question whether periodontal treatment could be a potential preventive intervention for adverse pregnancy outcomes including pre-eclampsia.

Prematurity, neurodevelopment and epigenetics

In humans, maternal infections during pregnancy and attendant inflammatory responses are a major cause of preterm birth, which has the potential to lead to specific neonatal problems, including cerebral white-matter damage [periventricular leukomalacia (PVL) and intraventricular haemorrhage (IVH)], cerebral palsy, respiratory distress syndrome (often leading to chronic lung disease), gastrointestinal and vision problems (retinopathy) (Pietz et al. 2004, Dammann et al. 2002, Hack 2005). Furthermore, increasing evidence suggests that the molecular and cellular inflammatory effector pathways that underlie the pathogenesis of preterm birth are also involved in both growth restriction and developmental problems ranging from respiratory distress to cognitive and learning disabilities (Dammann et al. 2002). Maternal intrauterine infection is considered a risk factor for developmental brain injuries in childhood. A variety of cytokines known to be toxic to developing brain cells have been isolated from mothers or children at risk for developmental disabilities, and these cytokines have been proposed as mediators of these injuries (Leviton et al. 1999). For example, foetal neurological tissues are especially susceptible to damage via cytokines, such as interferon gamma, that impair development of foetal neurons, and it has been suggested that cytokine exposure at a critical period of development may constitute a 'hit-and-run' mechanism for certain nervous system disorders that become manifest after a latency period (Brask et al. 2004, Kollas et al. 1992).

The mammalian central nervous system (CNS) is established through a temporally and spatially well-organized sequence of events during development and common multi-potent progenitors called neural stem cells mainly differentiate into neurons in the early developing brain and in astrocytes and oligodendrocytes in accordance with the progression of development (Qian et al. 2000, Sauvageot & Stiles 2002). It has been shown that chromosomal DNA in the neural progenitors undergoes epigenetic modification during this change in preference of differentiation and it is becoming more evident that intracellular programs such as epigenetic modification of chromosomal DNA, together with other factors, including cytokine signaling, can play multiple important roles in the regulation of cell type-specific gene expression during embryogenesis (Bird & Wolffe 1999, Edlund & Jessell 1999, Takizawa et al. 2001, Hsieh & Gage 2004, Abematsu et al. 2006). This concept is consistent with recent studies of genome structure and function that have revealed epigenetic control mechanisms such as methylation at CpG dinucleotides in gene promoters as important regulators of gene expression during brain development.

In our publications, we have demonstrated that maternal infection with periodontal pathogen *C. rectus* can result in placental translocation in a murine model. Data generated in pregnant mice suggest that maternal *C. rectus* infection can result in neonatal C. rectus brain infection that could be detected at P9 (i.e. 9 days after birth). It has been shown that the limited barrier properties of the developing cerebrovasculature may be further disrupted during a hypoxic-ischemic insult or in infection. Infection or hypoxia may increase the vascular permeability of weakened vessels and contribute towards pathological glial activation in affected areas indicating the possibility of foetal infection that can persist in the offspring. One might ask as whether these observed histopathological findings correlate to neurofunctional behaviours in the offspring.

Our studies have shown that *C. rectus* exposure in mice during the prenatal period does not result in overt motor impairment or general signs of ill health in adulthood. However, Figure 2 demonstrates that both male and female *C. rectus*-exposed F1 mice had significant reductions in rearing movements during a one-hour activity test, providing evidence that the early challenge led to alterations in exploratory activity in a novel open-field chamber (40 cm x 40 cm x 30 cm) crossed by a grid of photobeams (VersaMax system, AccuScan Instruments, Columbus, Ohio, USA).

The acoustic startle test was also used to assess auditory function and sensorimotor gating. For this study, mice were tested with a San Diego Instruments SR-Lab system. Measures were taken of the startle amplitude for each trial across a 65-msec sampling window.

The results showed that *C. rectus*-exposed F1 mice had a trend toward enhanced acoustic startle responses that closely approached significance (main effect of exposure, p=0.0571; Figure 3). Thus, the threat of maternal infectious exposure during pregnancy does not appear to be solely limited to effects on the duration of the pregnancy but also potentially to perinatal neurological growth and development.

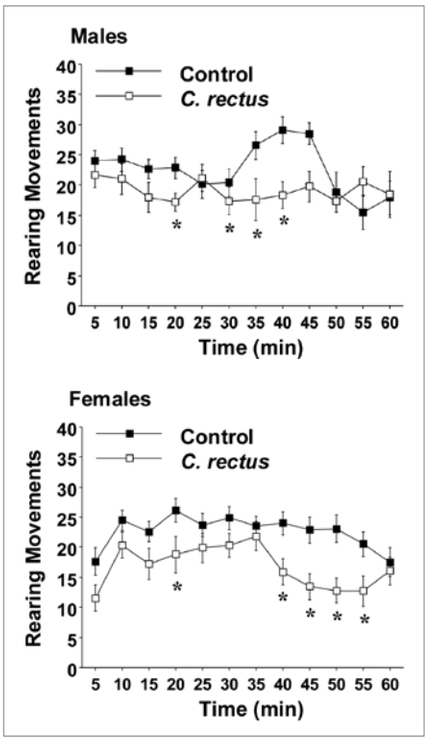

Figure 2.
Reduced rearing activity in *C. rectus* exposed mice. Data shown are means (± SEM) for each group for a one-hour test session. $p<0.05$. *C. rectus* group versus the control group at comparable time points.

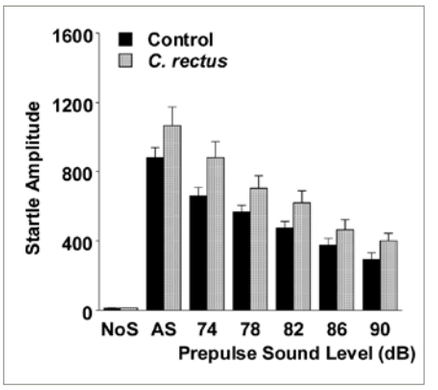

Figure 3.
Amplitude of the startle response following presentation of acoustic stimuli. Data shown are means (+SEM) for each group. Trials included no stimulus (No S) trials and acoustic startle stimulus (AS=40 msec; 120 dB) alone trials (trials with a prepulse stimulus (20 msec; either 74, 78, 82, 86 or 90 dB).

In addition, since Brain Derived Neurotrophic Factor (BDNF) has been implicated in adult neural plasticity, including learning and memory, we also explored methylation changes in E16.5 foetuses comparing *C. rectus* challenged to unchallenged mice. The methylation status of BDNF gene was analysed by pyrosequencing. DNA methylation analysis of brain samples collected from E16.5 fetuses (n= 7) after C. rectus maternal challenge in comparison to non-challenged mice (n= 7) is expressed for each of the three analysed DNA loci as percentage methylated cytosines over the sum of methylated and unmethylated cytosines. Data indicated an increase in DNA methylation for BDNF promoter region at position –105 (p=0.054) as shown in figure 4.

DNA methylation is likely to be an important mechanism controlling differential expression of BDNF during development and the disruption of which may be a contributing component of neurodevelopmental disorders (Weaver et al. 2004).

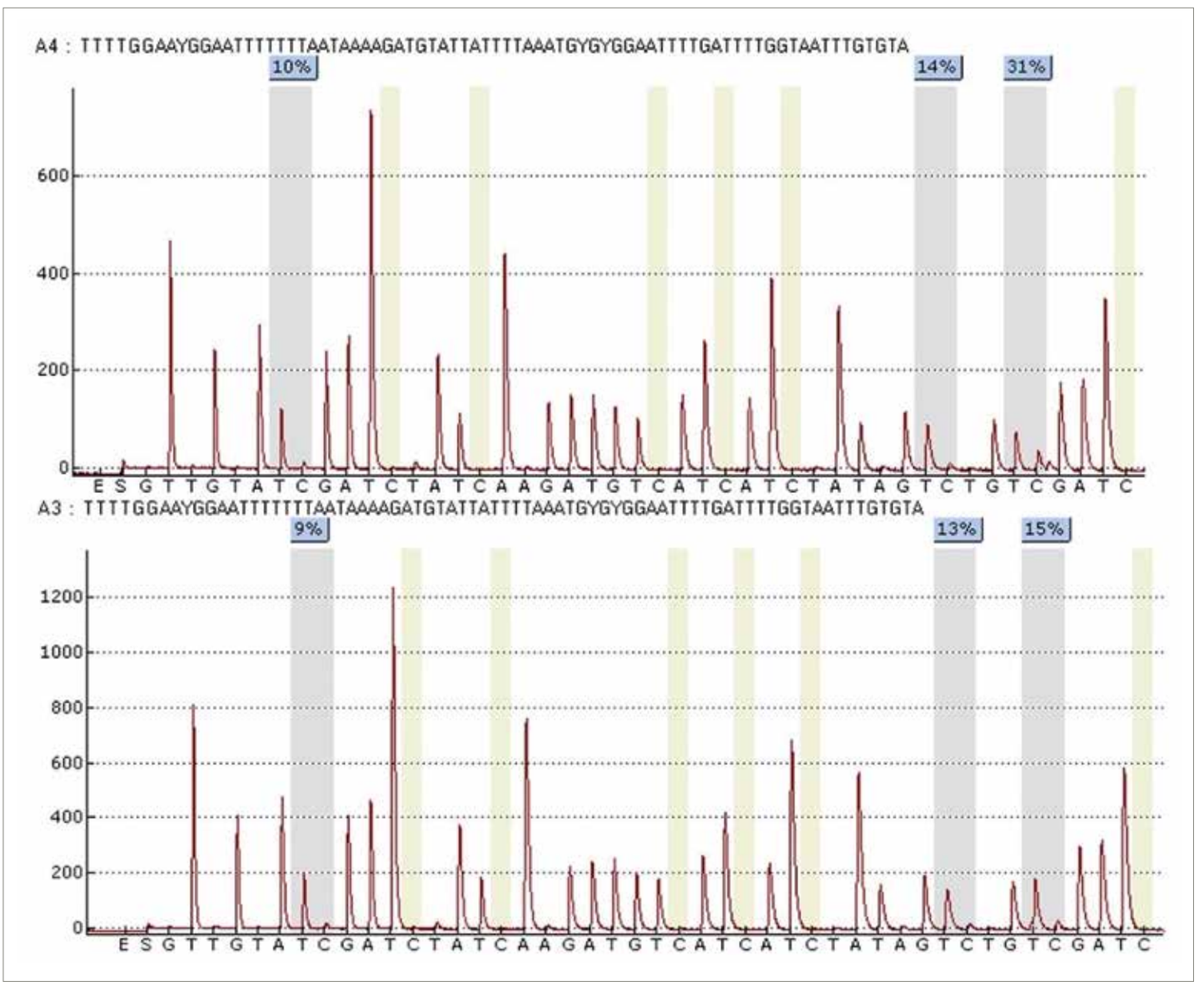

Figure 4.
The following sequence was pyrosequenced: TTTTGGAAYG GAATTTTTTT AATAAAAGAT GTATTATTTT AAATGYGYGG AATTTTGATT TTGGTAATTT GTGTA using Pyro Q-CpG software v1.0.9 (Pyrosequencing AB, Uppsala, Sweden). Data analysis was performed with Brown-Mood test in SAS. Significance was set at 5%.

Table 2. Birth outcomes after periodontal treatment (Offenbacher et al. 2009, modified).

	Control group	Treated group	*P value*
Less than 37 weeks	11.5%	13.1%	0.316
Birth weight (g)	3,241 +/- 590	3,227 +/- 612	0.694
Pre-eclampsia	8.4%	7.6%	0.548

Periodontal treatment for pregnant women

Following the promising results of several small intervention pilots, a few multi-centered randomized control trials have been performed to identify the potential efficacy of periodontal treatment on pregnant outcomes. We conducted a randomized clinical trial with more than 1,800 participants (Offenbacher et al. 2009). Although periodontal therapy resulted in statistically significant improvement for many periodontal clinical signs, the studies fail to demonstrate a different rate of adverse pregnant events between women with and without periodontal therapy (Table 2). The rate of preterm delivery for periodontal treatment group was 13.1% and 11.5% for control group. Michalowicz and colleagues assessed the effect of non-surgical periodontal therapy to more than 800 pregnant females (Michalowicz et al. 2006). The authors found that treatment of periodontitis in pregnant women improved periodontal condition and was safe, but did not significantly alter the rates of preterm birth, low birth weight, pre-eclampsia or foetal growth restriction. Although the reduction of tumor necrosis factor-alpha and interleukin-1-beta levels in gingival crevicular fluid after periodontal therapy for pregnant women was identified, the rates of preterm birth or low birth weight did not differ in relation to periodontal treatment (Kaur et al. 2014).

Michalowicz et al. reviewed randomized controlled trials to determine whether periodontal therapy reduces rates of preterm birth and low birth weight (Michalowicz et al. 2013). The authors concluded that non-surgical periodontal therapy, scaling and root planing did not improve birth outcomes in pregnant women with periodontitis. A possible reason for non-effectiveness of periodontal treatment on pregnancy outcomes would be timing of periodontal care. Periodontal therapy for women in pregnancy may be too late to affect birth outcomes. It is proposed that periodontal treatment before pregnancy may reduce the rates of adverse pregnancy outcomes (Xiong et al. 2011). Lopez et al. pointed out that periodontal treatment used in several randomized controlled clinical trials was not effective in eliminating periodontal diseases (López et al. 2015). The mechanisms by which maternal periodontal infection and following immune protection mediate pregnancy risk are not fully understood. Further research to clarify the role of foetal infectious exposure involving preterm outcome is needed.

It is widely known that pregnancy is associated with an increased risk of periodontal diseases. Increases in female sex steroids led to preferential colonization by black-pigmented *Bacteroides*, especially *Prevotella intermedia* (Kumar 2013). It was also reported that the estrogen level determined the magnitude of gingival inflammation developed against microbial plaque during pregnancy (Gürsoy et al. 2013). A systematic review confirmed increased inflammation throughout pregnancy in comparison to post-partum or non-pregnant women, without a concomitant increase in plaque levels (Figuero et al. 2013). However, hormonal changes during pregnancy might not interfere in treatment outcomes in women and that periodontal health could be reestablished irrespective of the hormonal challenge taking place during pregnancy (Moreira et al. 2015).

Confirming the safety of dental care in pregnancy is an important issue. Michalowicz and colleagues randomly assigned 823 women with periodontitis to receive scaling and root planing, either at 13 to 21 weeks' gestation or up to three months after delivery (Michalowicz et al. 2008). The authors found that dental treatment in pregnant women at 13 to 21 weeks' gestation did not increase a risk of experiencing serious medical adverse events or adverse pregnancy outcomes. Findings in most dental studies with pregnant women are consistent with this result, which indicates that dental treatment in pregnancy would be safe.

A consensus report of the Joint European Federation of Periodontology (EFP)/ American Academy of Periodontology (AAP) Workshop recommended that pregnant women receive education about preventing and treating periodontal diseases both for women's own oral health and for the future oral health of their children in addition to providing pregnant women with oral-health care (Sanz & Kornman 2013). Particularly for pregnant females with periodontitis, professional intervention should be the standard non-surgical periodontal therapy aimed at reducing subgingival biofilm and signs of periodontal inflammation. It was suggested that major factors predicting the utilization of dental services during pregnancy were perceived need, habit of regular dental visits, and access to dental services (Amin & ElSalhy 2014). Regular check-up at the dental surgery may be important for not only pregnant females but also women before pregnancy.

Although periodontal treatment overall had no significant effect on preterm birth or low birth weight, periodontal therapy for pregnant women could potentially reduce the risks of perinatal outcomes, especially in mothers with high risks (Schwendicke et al. 2015). The effect of periodontal treatment on the prevention of preterm delivery and other complications during pregnancy may be influenced by its effect on the bacterial load and on the host inflammatory response (Zi et al. 2015). Periodontal treatment, when appropriately administered and adequately performed during pregnancy, appears to be safe for the mother and the foetus, and in some populations can control or eliminate periodontal infection and reduce the risk of preterm birth (López et al. 2015). Oral health is an important part of systemic health and so should be well maintained during pregnancy.

SUMMARY

EVIDENCE FROM MANY EPIDEMIOLOGICAL STUDIES indicates an association between poor oral health and adverse pregnancy outcomes such as preterm birth, low birth weight and pre-eclampsia. Periodontal infection might be an independent risk factor for adverse pregnancy events, while periodontal treatment during pregnancy does not improve pregnancy outcomes. Although several possible theories connecting periodontitis and adverse pregnancy outcomes have been suggested, the underlying mechanisms have not been clarified. It appears that understanding the fundamental pathogenesis of oral-infection-mediated pregnancy complications would be a critical step in identifying appropriate therapeutic targets. Because increased female sex steroids lead to gingival inflammation, oral healthcare has to be continued during pregnancy. Dental therapy has been shown to be safe for pregnant women and the baby.

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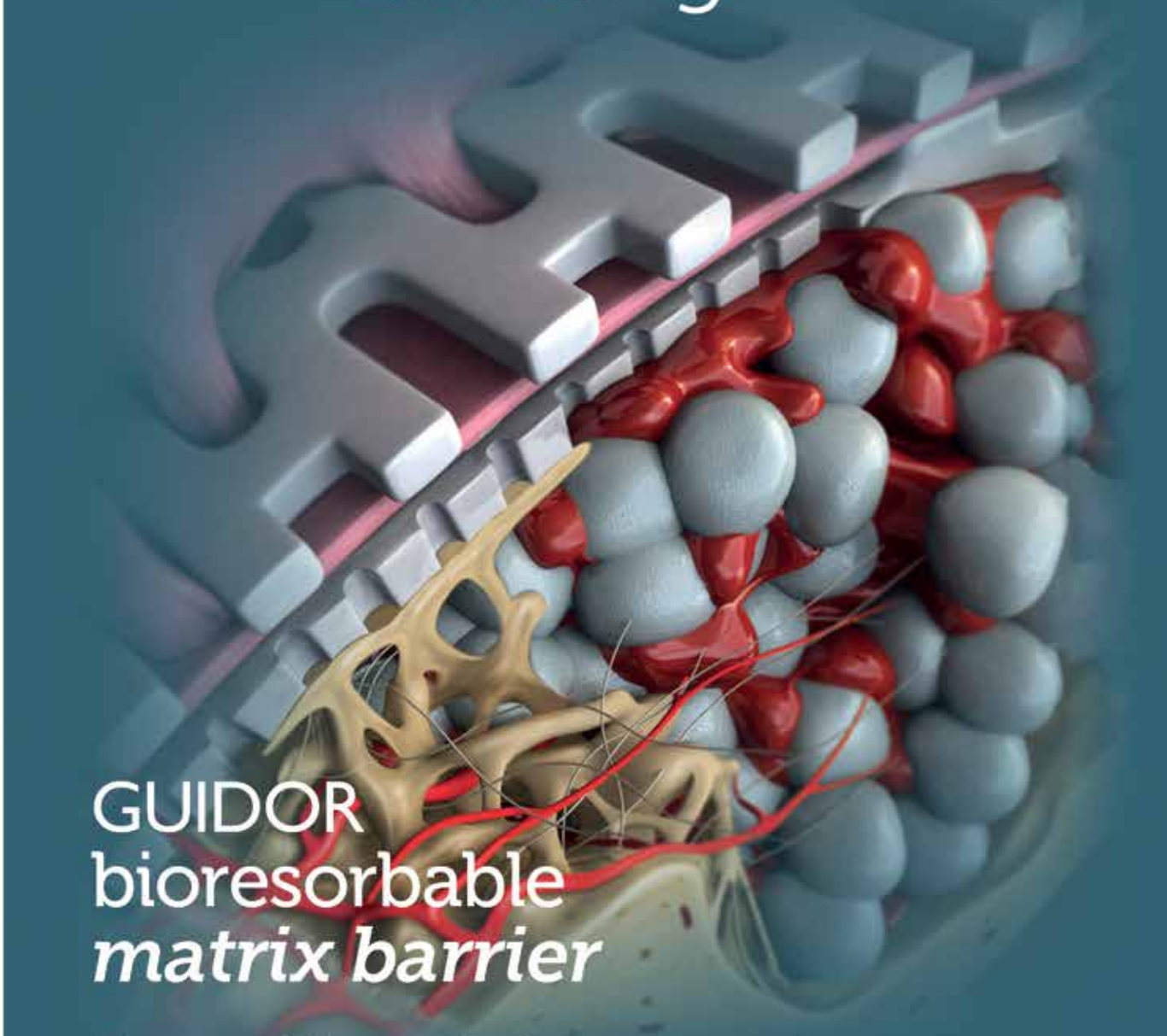

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DIABETES AND PERIODONTAL DISEASES: THE BIDIRECTIONAL ASSOCIATION AND ITS IMPLICATIONS.

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ABSTRACT

DIABETES MELLITUS (DM) and periodontitis are common, complex, chronic diseases with an established bidirectional relationship. Poorly controlled DM is associated with an increased prevalence and severity of periodontitis, being acknowledged as a true risk factor for periodontitis onset and progression. On the other hand, there is growing evidence that chronic infectious diseases, such as periodontitis, could increase the risk for DM development and compromise glycaemic control in people with DM. In addition, non-surgical periodontal treatment can improve glycaemic control in patients with DM. Therefore, this bidirectional association may have relevant implications for health professionals, for DM and periodontitis patients, as well as for the general population. Due to these implications, dental professionals may play an important role in the management of DM patients, not only by rendering periodontal care in people with DM, but also helping identify patients with undiagnosed DM or at high risk of developing it, by the use of appropriate screening tools. The aim of this narrative review was (1) to address the mechanistic links that have been proposed as basis of the periodontitis-DM relationship; (2) to report the epidemiological evidence from cross-sectional and longitudinal studies; and (3) to describe the impact of periodontal care on DM control. Recommendations for medical and dental professionals, as well as recommendations for patients/public are proposed.

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INTRODUCTION

What is diabetes mellitus?

Diabetes mellitus (DM) represents a group of metabolic diseases characterized by hyperglycaemia, associated with defects in insulin secretion, insulin action or both. Chronic hyperglycaemia is associated with damage, dysfunction and/or failure in different organs, including eyes, nerves, kidney, heart or blood vessels.

A diagnosis of DM is normally established if Fasting Plasma Glucose (FPG) is ≥ 126 mg/dl or if glycated haemoglobin (HbA1c) is ≥ 6.5% (American Diabetes Association 2003, American Diabetes Association 2013).

A classification of conditions and risk categories within DM is presented here:

- **DM type 1** normally presents in thin young persons, with acute symptoms, together with ketosis and loss of weight. In 90% of the cases, organ-specific autoimmune markers are present [e.g. anti-GAD (antibodies against enzyme glutamic acid decarboxylase) or ICA (antibodies against islet cells of the pancreas)]. An idiopathic form, with no immune biomarkers is found in African and Asian ethnic groups.
- **DM type 2** has a silent onset and no ketosis or family aggregation. It is associated to overweight or obesity, and characterized by deficit in insulin secretion and resistance to its action. No genetic markers are evident.
- **Gestational DM** and **DM in pregnancy** are defined as an alteration of glucose metabolism, detected during pregnancy, in previously healthy women (United Nations 2013)
- **Other types of diabetes** include those associated with genetic defects (either in beta cells function or in insulin action), endocrine diseases (drug- or infection induced), exocrine pancreas diseases, or genetically or immune-driven conditions, including LADA (*latent autoimmune diabetes of adult*) or MODY (*maturity onset diabetes of the young*).

How important is diabetes mellitus?

Worldwide prevalence

According to IDF Diabetes Atlas (International Diabetes Federation 2015), the global prevalence of diabetes in adults (20-79 years) is 8.8% (7.2-11.4%), and it is estimated to increase to 10.4% (8.5-13.5%) by 2040. This represents 415 million adults with diabetes in 2015 and an expected figure of 642 million in 2040. Hyperglycaemia in pregnancy (20-49 years) affects 16.2% of live births and impaired glucose tolerance (20-79 years) has a global prevalence of 6.7%. Type 1 diabetes (0-14 years) affects 542,000 with a yearly increase of 86,000.

The information from Spain, thanks to the excellent study di@bet.es (Soriguer et al. 2012), calculated a total prevalence of DM type 2 of 13.79%, with diagnosed DM representing 7.78% and unknown DM 6.01%.

Human cost: complications

The IDF Diabetes Atlas has estimated the number of deaths caused by diabetes in 2015 at 5.0 million (International Diabetes Federation 2015). But, in terms of human cost, the relevance of DM is based on the importance of the associated complications.

DM is associated with frequent complications, which have been classically summarized as retinopathies, nephropathies, peripheral and autonomic neuropathies, and cardiovascular diseases (including hypertension and lipid metabolism alterations). These complications are briefly described here:

- DM, due to hyperglycaemia, may affect small blood vessels (arterioles, venules and capillaries), which is known as diabetic microangiopathy (MAD), and it is responsible for retinopathies, diabetic nephropathy and even diabetic neuropathy. Among microvascular complications, diabetic nephropathy has the highest clinical relevance, as it is the main cause of chronic renal disease.
- Diabetic neuropathy may affect both peripheral and autonomic nervous systems, being a condition directly related to hyperglycaemia. Diabetic autonomic neuropathy has relevant clinical implications, since it may affect multiple organs (eyes, sweat glands, urinary bladder, sexual organs, oesophagus, gastrointestinal system, cardiovascular system, etc.).
- Cardiovascular diseases represent one of the most relevant complications of DM, normally associated with coronary atherosclerosis. Myocardial infarction is 3-5 times more frequent in persons with diabetes. The synergistic effect with other risk factors is very relevant, including obesity, dyslipidemia and hypertension, leading to the metabolic syndrome concept.
- Peripheral vascular disease may have a very early onset in people with diabetes, being one of the main risk factors for diabetic foot. Dermal complications include diabetic dermopathy or necrobiosis lipoidica diabeticorum.
- In recent years, periodontal diseases have also been considered a relevant complication of diabetes (Loe 1993), and this will be discussed in the present paper.

Financial cost

According to the IDF Diabetes (International Diabetes Federation 2015), the health expenditure due to diabetes in adults is USD 673 billion in 2015, representing 12% of the global health expenditure.

In Spain, the overall direct cost per year has been estimated at €5.1 billion, with an additional €1.5 billion for the indirect costs derived from the management of its complications (Lopez-Bastida et al. 2013).

MECHANISTIC LINKS BETWEEN PERIODONTAL DISEASES AND DIABETES

Mechanisms underlying the effect of DM on periodontitis

Periodontal microbiota

Although early studies suggested the existence of distinct subgingival microbial profiles (Zambon et al. 1988), it does not appear that the microbial microbiota of people with diabetes differs from that of healthy individuals (Yuan et al. 2001, Lalla et al. 2006b, Ebersole et al. 2008). However, this conclusion came from studies mainly based on conventional methods, such as checkerboard DNA-DNA hybridization and polymerase chain reaction (PCR), instead of looking at the entire bacterial community. Recent studies using high-throughput 16S rDNA pyrosequencing have detected that subjects, with and without DM, harboured bacteria at several taxonomic levels with significantly different prevalence or abundance; certain genus being more prevalent in patients with healthy gums and diabetes (genus of Neisseria), or in subjects with both periodontitis and diabetes (Tannerella forsythia) than in their non-diabetic counterparts (Casarin et al. 2013, Zhou et al. 2013).

Cytokines and matrix metalloproteinases (MMP)

Inflammation is a central feature of both diabetes and periodontal diseases, and inflammatory processes are up-regulated in the periodontal tissues of patients with diabetes. Both type 1 and type 2 DM are associated with elevated gingival crevicular fluid (GCF) levels of inflammatory mediators, such as interleukin (IL)-1β and prostaglandin E2 (PGE2), when compared to non-diabetic controls matched with regard to periodontitis severity (Salvi et al. 1997, Engebretson et al. 2004, Mohamed et al. 2015).

Animal studies in diabetic mice corroborate these findings and highlight the role of tumour necrosis factor-α (TNF-α) in the enhanced immune response to periodontal bacteria (Graves et al. 2004, Liu et al. 2006). Recently, the concentration of a broad panel of cytokines in GCF from healthy and diseased sites of subjects with uncontrolled type 2 DM and of non-diabetic subjects has been studied (Duarte et al. 2014). Higher concentrations of TNF-α, granulocyte macrophage colony-stimulating factor-α, IL-6 and IL-12 were found in healthy and diseased sites of patients with diabetes, suggesting that the increased levels of proinflammatory mediators could partially explain the greater susceptibility of DM subjects to periodontal breakdown.

It has been hypothesized that DM-related alterations in GCF levels of MMPs, and/or their inhibitors, may be part of the mechanism by which diabetes affects periodontal health. However, no differences for MMP-8, MMP-13 and tissue inhibitor of MMP-1 were detected between systemically healthy and type 2 DM subjects with periodontitis, gingivitis or periodontal health (Kardesler et al. 2010). Data from gingival/periodontal tissue biopsies present conflicting results (Kumar et al. 2006, Hardy et al. 2012).

Alveolar bone homeostasis

The receptor activator of nuclear factor-kappa B ligand (RANKL) is responsible for stimulation osteoclast differentiation and bone resorption. RANKL can be blocked by osteoprotegerin (OPG), preventing its potential deleterious effects. In periodontitis subjects, RANKL is up-regulated while OPG is down-regulated, resulting in an increased RANKL/OPG ratio (Belibasakis & Bostanci 2012)). Several studies have demonstrated that the RANKL/OPG ratio is higher in poorly controlled diabetic patients with periodontitis compared to well-controlled or non-diabetic subjects with similar periodontal status (Santos et al. 2010, Ribeiro et al. 2011).

Advanced glycation end-products (AGEs)

AGEs are resulting products after non-enzymatic glycation and oxidation of proteins and lipids that accumulate in plasma and tissues. Increased blood-glucose levels lead to excessive accumulation of AGEs in serum, cells and tissues, including the gingiva and the periodontium (Schmidt et al. 1996). Binding of AGEs to their cell surface receptors, RAGEs, activates host cells such as monocytes and endothelial cells to release pro-inflammatory cytokines (Lalla et al. 2001), and it is recognized as a major cause of diabetic complications (Sorci et al. 2013). Blockade of RAGEs significantly suppressed alveolar bone loss in diabetic mice infected with periodontal pathogens (Lalla et al. 2000), indicating that AGE-RAGE interaction may lead to the exacerbated inflammatory response contributing to the destruction of the periodontal tissues. Besides diabetes, periodontal inflammation alone leads to accumulation of AGEs in periodontal tissues, demonstrating an interaction between diabetes and periodontitis (Chang et al. 2013, Zizzi et al. 2013).

Reactive oxygen species (ROS)

ROS include free radicals (e.g. superoxide O2- and hydroxyl radicals OH-), non-radical oxygen species [e.g. hydrogen peroxide (H2O2)], and reactive lipids that are generated by physiological cellular functions such as neutrophil phagocytosis. In diabetes patients, leukocytes release elevated amounts of ROS compared with systemically healthy individuals, which are thought to be the major player in microvascular complications (Devaraj & Jialal 2000, Gorudko et al. 2012). The increase in vascular permeability caused by hyperglycemia and leukocyte-induced microvascular damage, may contribute to periodontal tissue destruction in diabetes (Sima et al. 2010, Gyurko et al. 2006).

Mechanisms underlying the effect of periodontitis on DM

Periodontal microbiota

Whether the subgingival microbial profile has any impact on diabetes, or glycaemic control, has not been investigated in depth. Just one study in Japan, in which patients with chronic periodontitis and type 2 DM received non-surgical periodontal therapy, addressed the issue (Makiura et al. 2008). After therapy, it was observed that Porphyromonas gingivalis, particularly the strain with type II fimbriae, was detected more frequently in those subjects who had increased HbA1c values when compared to those with decreased values relative to baseline examination. This finding suggests that glycaemic control in patients with periodontitis and DM could be influenced by the presence of P. gingivalis.

Inflammatory factors and oxidative stress

Periodontitis is associated with elevated levels of pro-inflammatory and pro-thrombotic mediators in serum, such as C-reactive protein (CRP), TNF-α and IL-6 (Paraskevas et al. 2008, Kebschull et al. 2010), and dysregulation of the peripheral cytokine pool is now considered a central pathogenic factor in diabetes (Kolb & Mandrup-Poulsen 2010). Thus, it is possible that the systemic inflammation associated with the local inflammatory response triggered by periodontal microbiota leads to insulin resistance. For example, TNF-α, which is elevated in plasma of patients with periodontitis (Engebretson et al. 2007), is known to promote insulin resistance by interfering with insulin signalling (Abbatecola et al. 2004, Gupta et al. 2005). Also, periodontitis has proven to aggravate pancreatic β-cell failure in diabetic mice (Liu & Zhang 2016).

Oxidative stress and mitochondrial dysfunction have been also presented as shared factors in the pathogenesis of periodontitis and DM, as biochemical markers of systemic oxidative stress are elevated in both diseases (Bullon et al. 2009, Bullon et al. 2014). In addition, these markers have been positively correlated with CRP in periodontitis patients (D'Aiuto et al. 2010). However, although there are longitudinal data from epidemiological studies, there is little evidence for the exact mechanisms to explain how periodontitis could impact on the disease processes of DM. The various pathways proposed to link diabetes and periodontitis are illustrated in Figure 1.

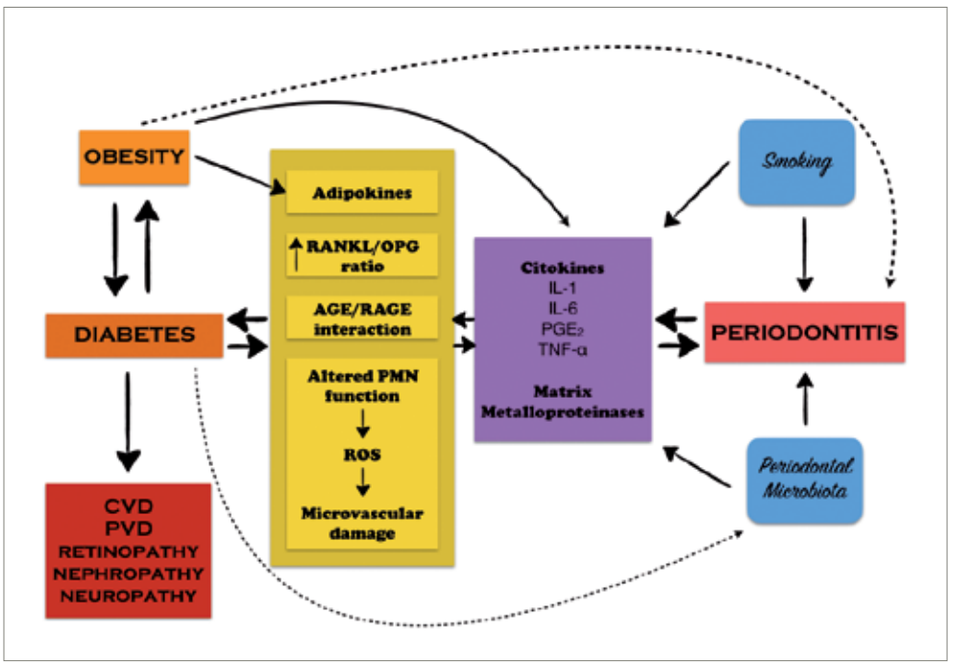

Figure 1.
Schematic representation of the two-way relationship between diabetes and periodontitis. Partially adapted from Preshaw et al. (2012).

Table 1. Selected studies evaluating diabetes mellitus as exposure for periodontitis.

Reference	Study Design	DM Type	Sample	Results
(Hugoson et al. 1989)	Cases & Controls	Type 1	154 diabetic and 77 non-diabetic subjects	Long-duration DM subjects presented increased severity of periodontitis both as ABL and AL
(Shlossman et al. 1990)	Cross-Sectional	Type 2	3219 Pima Indians	Mean AL and ABL was higher in DM for all age groups
(Nelson et al. 1990)	Prospective study	Type 2	701 Pima Indians were evaluated longitudinally	DM predicted a greater incidence of periodontitis (RR=2.6)
(Emrich et al. 1991)	Cross-sectional	Type 2	1342 Pima Indians	DM, age and calculus were identified as risk indicators (OR=2.8 for suffering periodontitis)
(Oliver & Tervonen 1993)	Cases & Controls	Types 1 and 2	114 diabetic patients	AL and tooth loss was comparable between groups. Prevalence of sites with PPD≥4 mm was higher for DM
(Thorstensson & Hugoson 1993)	Cases & Controls	Type 1	83 DM subjects and 99 controls	DM patients had more PPD≥6 mm and more extensive ABL
(Bridges et al. 1996)	Cases & Controls	Non-specified	233 men (118 diabetic and 115 non-diabetic)	PPD and AL were significantly higher in DM
(Lalla et al. 2007b)	Cases & Controls	Types 1 and 2	350 DM children and adolescents, 350 controls	Children with DM had significantly more gingival inflammation and a higher number of teeth with AL
(Hodge et al. 2012)	Cases & Controls	Type 1	34 well controlled DM sub-jects, 169 poorly controlled DM subjects and 112 non-diabetic controls	Prevalence of periodontitis was higher in all DM subjects. ORs for the well controlled and poorly controlled groups were 1.35 and 1.58 respectively for suffering periodontitis

DM, diabetes mellitus; **ABL**, alveolar bone loss; **AL**, attachment loss; **OR**, odds ratio; **RR**, relative risk; **PPD**, probing pocket depth.

EPIDEMIOLOGICAL EVIDENCE

Evidence for DM as a risk factor for periodontitis

The role of DM as a risk factor for periodontitis has been debated for decades. Numerous studies (Table 1) have identified a higher prevalence and severity of periodontitis in patients with type 1 DM, particularly in subjects with a long duration of DM and poor metabolic control (Hugoson et al. 1989, Oliver & Tervonen 1993, Thorstensson & Hugoson 1993, Lalla et al. 2007a, Hodge et al. 2012). For type 2 DM, the evidence is even stronger, especially in certain subgroups, such as African Americans or the Pima Indians, who have an extremely high prevalence of type 2 DM (Fernandes et al. 2009, Bandyopadhyay et al. 2010, Shlossman et al. 1990, Nelson et al. 1990, Emrich et al. 1991, Bridges et al. 1996). Of particular relevance, longitudinal studies have clearly showed that DM precedes periodontitis, a finding supporting causality (Nelson et al. 1990, Bandyopadhyay et al. 2010), and that poorer glycaemic control leads to an increased risk for alveolar bone loss and periodontitis progression (Taylor et al. 1998). However, it should be stressed that the association between DM and periodontitis is just limited to those cases with poorly controlled DM, as neither well-controlled DM nor pre-diabetes have been related to a greater prevalence or severity of periodontitis (Kowall et al. 2015, Garcia et al. 2015).

The clinical and radiographic assessment of a type 2 DM patient (Clinical case 1) with poor metabolic control and periodontitis is presented in Figures. 2, 3 and 4.

Figure 3.
Clinical case 1: periodontal chart. Note the attachment loss and presence of deep pockets, as well as suppuration on certain sites.

Figure 2.
Clinical case 1: general view of a 40-year-old man with poorly controlled diabetes mellitus type 2 and generalized moderate, localized severe, chronic periodontitis.

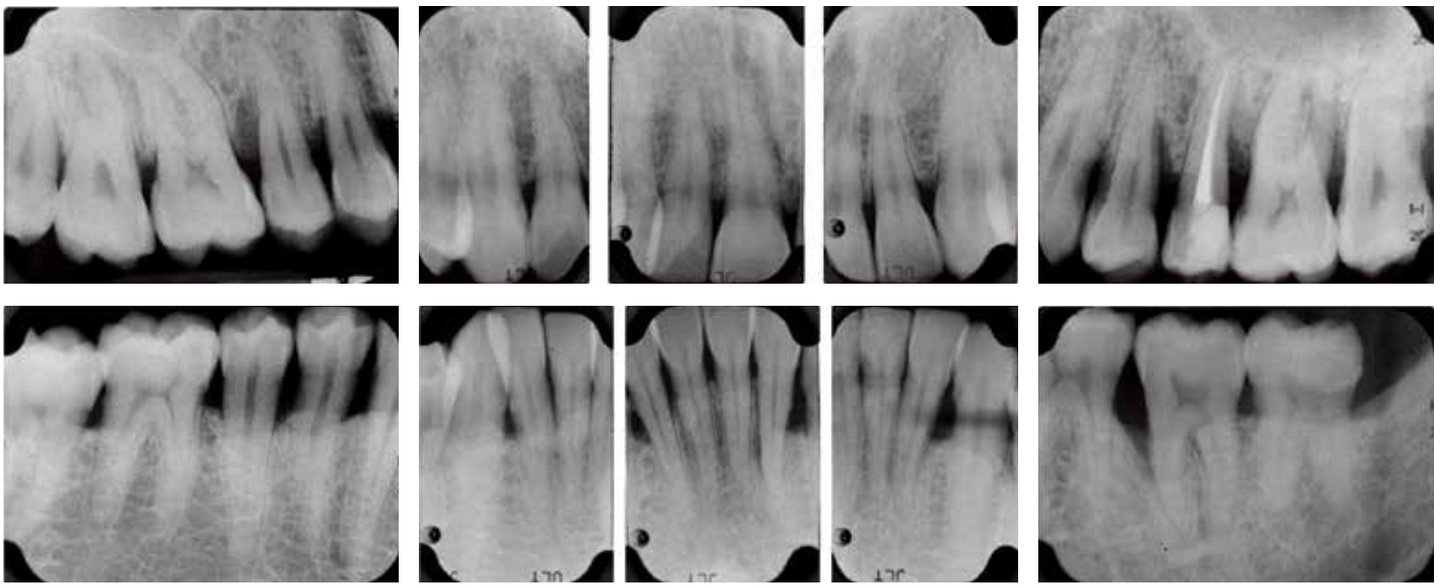

Figure 4.
Clinical case 1: periapical radiographs. Note the presence of several intrabony defects.

Studies performed in children and adolescents with either type 1 or 2 DM documented more pronounced gingival inflammation and clinical attachment level (CAL) loss than their matched controls (Lalla et al. 2006a), establishing the age of onset of DM manifestations in the periodontium from 6 years old (Lalla et al. 2007a). A case (Clinical case 2) is presented showing the periodontal status of a teenager suffering from type 1 DM with poor metabolic control (Figures. 5, 6 and 7).

Meta-analysis of cross-sectional and longitudinal studies indicated a significantly higher mean CAL loss of 1 mm [95% confidence interval (CI): 0.15-1.84] and a greater mean probing pocket depth (PPD) of 0.46 mm (0.01-0.091) of type 2 DM patients compared with control subjects (Chavarry et al. 2009).

Figure 5.
Clinical case 2: overview of a 18 year old female with diabetes mellitus type 1 and severe aggressive periodontitis. Courtesy of Dr. Estefanía Laguna.

Figure 6.
Clinical case 2: periodontal chart of patient.

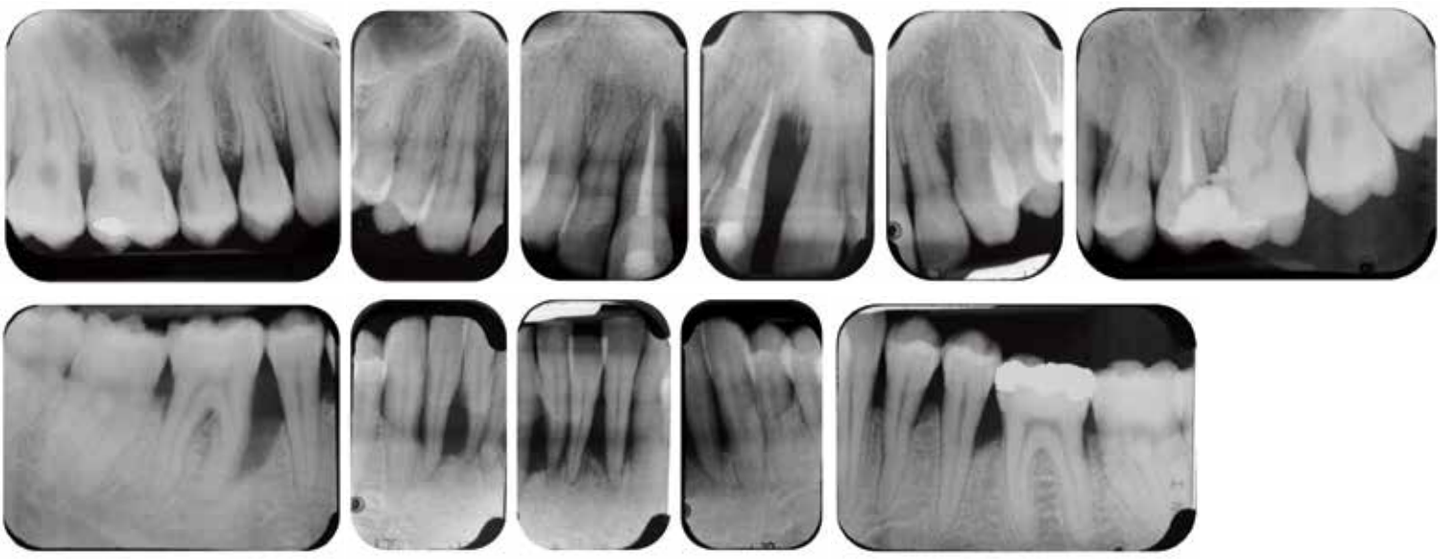

Figure 7.
Clinical case 2: periapical radiographs of patient.

Evidence for the effects of periodontitis on DM

Periodontitis may also impact upon DM. The most extensively explored effects are related to glycaemic control, development of complications and onset of DM (Borgnakke et al. 2013).

Longitudinal studies performed in the Pima Indian population demonstrated that severe periodontitis (expressed either by CAL or radiographic bone loss) was associated with 4.2-13.6 times higher risk for poor glycaemic control (Taylor et al. 1996). Large population studies in Japan and Germany have associated deterioration in the periodontal status with a significant increase in HbA1c throughout 5-10 years, to the point that each additional mm in mean PPD corresponded with an 0.13% increase in HbA1c (Saito et al. 2004, Demmer et al. 2010).

Among patients without known DM, poorer periodontal health has also been associated with an increased risk for incident type 2 DM (Saito et al. 2004, Demmer et al. 2008, Morita et al. 2012). In USA population, people with gingivitis had 40% increased odds of developing DM, while those with periodontitis had 50% elevated risk (Demmer et al. 2008). In a Japanese population, those presenting sites with PPD≥6 mm had 3.45 times higher risk of developing DM (Morita et al. 2012).

People with DM are particularly susceptible to micro- and macro-vascular complications, which are primarily responsible for the increased morbidity and mortality associated with this condition. It has been proposed that periodontitis could be related to the development of complications in patients with DM, particularly nephropathy, ischemic heart disease and ictus (Saremi et al. 2005, Shultis et al. 2007, Thorstensson et al. 1996). Cross-sectional studies have associated other DM complications such as retinopathy or neuropathic foot ulceration with periodontitis, but longitudinal data is missing (Noma et al. 2004, Abrao et al. 2010).

Periodontitis has also been evaluated for a potential role in the development of gestational diabetes mellitus (GDM). In a case-control study with 53 pregnant women with GDM and 106 without GDM, and after adjusting for confounding variables, the odds ratio (OR) for periodontitis and GDM was calculated to be 2.6 (95% CI, 1.1-6.1), with higher adjusted ORs for the highest quartiles according to periodontitis severity (Xiong et al. 2009). A recent systematic review with meta-analysis of observational studies showed that periodontitis is associated with an increased risk of GDM by 66% (OR=1.66); with an even more robust association when considering only high-quality case-control studies that adjusted for potential confounders (OR=2.08). Although the authors indicated that the diagnostic criteria for periodontitis and GDM varied widely among studies, the results suggested an association between the two diseases (Abariga & Whitcomb 2016).

PROPOSED BENEFITS OF PERIODONTAL TREATMENT FOR DM

Periodontal treatment and glycaemic control

Periodontal treatment resolves inflammation and reduces circulating cytokines among individuals with diabetes (Artese et al. 2015) and may thus reduce hyperglycemia in these subjects. Several randomized clinical trials (RCTs) have evaluated the effect of periodontal therapy on people with DM, with HbA1c being the most commonly used clinical endpoint. These trials have reported reductions in HbA1c ranging from 1.11% (Kiran et al. 2005) to 0.05% (Katagiri et al. 2009).

More than 10 systematic reviews with meta-analysis (Table 2) on the effectiveness of periodontal treatment to improve glycaemic control have been published, estimating an average reduction of 0.46% in HbA1c in patients with DM (Faggion et al. 2016). The consensus report of the Joint European Federation of Periodontology (EFP)/American Academy of Periodontology (AAP) Workshop on Periodontitis and Systemic Diseases recommended that these results should be interpreted with caution, as most of the studies were small unpowered trials, highlighting the need for larger clinical investigations (Engebretson & Kocher 2013, Chapple & Genco 2013).

Table 2. Selected systematic reviews evaluating the effect of periodontal therapy on HbA1c levels.

Reference	Study Designs	Number of patients (range)	Follow-up (range; weeks)	Results
(Janket et al. 2005)	CCTs, RCTs	10-113	2-96	Periodontal therapy decrease HbA1c levels by non-significant 0.38% for both type 1 and type 2 DM. A reduction of 0.71% was observed among just type 2 DM
(Darre et al. 2008)	CCTs, RCTs	20-72	2-104	MA of 9 studies showed significant improvement of HbA1c with periodontal treatment
(Teeuw et al. 2010)	CCTs, RCTs	44-165	12-36	MA of 5 studies showed a weighted mean difference in HbA1c of -0.40% in type 2 DM for at least 3 months
(Simpson et al. 2010)	RCTs	30-113	12-24	MA of 3 RCTs showed SS reduction in HbA1c following periodontal treatment (-0.40%)
(Sgolastra et al. 2013)	RCTs	40-126	12-24	MA of 5 RCTs showed that SRP was effective in reducing HbA1c and FPG
(Corbella et al. 2013)	RCTs	NR	12-24	MA of 15 studies showed periodontal treatment reduced HbA1c by –0.38% after 3-4 months and of -0.31% after 6 months
(Liew et al. 2013)	RCTs	40-154	12-24	MA of 6 studies showed SS reduction in HbA1c (-0.41%)
(Engebretson & Kocher 2013)	RCTs	40-165	12-36	MA of 9 studies demonstrated a treatment effect of -0.36%
(Sun et al. 2014)	RCTs	40-157	12-36	MA of 6 studies demonstrated a mean periodontal treatment effect of 1.03% in HbA1c

CCT, controlled clinical trial; **RCT**, randomized clinical trial; **DM**, diabetes mellitus; **HbA1c**, glycated haemoglobin; **MA**, meta-analysis; **SS**, statistically significant; **SRP**, scaling and root planing; **FPG**, fasting plasma glucose.

In particular, a multicentre RCT including 514 patients was published just a few months after the Joint Workshop, reporting that non-surgical periodontal therapy did not improve glycaemic control in patients with type 2 DM and moderate to advanced chronic periodontitis (Engebretson et al. 2013). However, this study has relevant methodological problems that render the conclusions doubtful and led to a wave of letters to the editor and critical reviews (Merchant et al. 2014, Chapple et al. 2014, Vergnes et al. 2014, Borgnakke et al. 2014). It is important to highlight that, in the referred study, the periodontal therapy provided failed to clinically manage the periodontal infection and associated inflammatory burden, as the residual plaque levels (72%) and bleeding scores (42%) are far away from the accepted standard of care. In addition, most of the subjects included presented a control of diabetes that was predominantly good at baseline (mean HbA1c level 7.8%), with less than 60% of patients having HbA1c levels greater than 8.0%. With the mean HbA1c value close to the therapeutic target, a substantial improvement in HbA1c levels is difficult to expect. A third significant problem was the mean body mass index (BMI) of the participants, which was approximately 34 kg/m2, so most of them were obese (≥30 kg/m2). A recent systematic review concluded that there were significant differences in the metabolic response after periodontal therapy between obese and normal-weight patients (Papageorgiou et al. 2015), which would have masked the anti-inflammatory effect of periodontal treatment. Thus, it is possible that in this study most of the subjects were resistant to the elimination of the periodontitis-related systemic inflammation due to the overwhelming influence of obesity.

A recent prospective cohort study including more than 120,000 subjects with DM and periodontitis treated in the VAs (Veteran Administration) medical centres in the USA, reported that periodontal treatment reduced HbA1c by 0.02% to 0.074% after initial treatment and an average of 1.7 years of supportive periodontal therapy respectively (Merchant et al. 2016). Beneficial effects were greater among never-smokers and individuals with higher baseline HbA1c levels. Long-term periodontal care increased the likelihood of individuals achieving proper diabetes control by 5% and 3% at the HbA1c <7% and <9% thresholds, respectively. These findings compelled the authors to conclude that periodontal treatment improved long-term glycaemic control among individuals with type 2 DM and periodontitis.

At this moment, when all the available evidence is combined, the effects of periodontal treatment on HbA1c still points to an improvement in glycaemic control in diabetic patients, although attention should remain on the evolution of these data as several trials are still on going.

Clinical relevance of the reduction in HbA1c

The benefits derived from the control of hyperglycaemia are clear in terms of preventing its complications. Each percentage point of decrease in HbA1c results in a reduction in risk of micro-vascular complications of about 35% (Stratton et al. 2000). Furthermore, an average reduction in HbA1c of 0.20% is associated with a reduction in all-cause mortality of approximately 10% (Khaw et al. 2004).

Therefore, it is reasonable to expect that a reduction in HbA1c of approximately 0.4%, found to be associated with non-surgical periodontal treatment in patients with diabetes, would have clinically significant effects on systemic health, especially in patients with poorly controlled diabetes. Of course, trials evaluating the effect of periodontal therapy on diabetic complications are needed.

SUMMARY

CONVINCING EVIDENCE EXISTS to support the fact that DM (types 1 and 2, particularly if poorly controlled) is a risk factor for periodontitis, increasing the risk of onset and progression of periodontitis. Evidence also suggests that advanced periodontitis compromises glycaemic control. It appears that this is a bidirectional relationship, and that patients with severe periodontitis and DM suffer from more cardio-renal mortality and microalbuminuria than patients with DM and no periodontitis. Periodontal treatment has been associated with improvements in glycaemic control in the short term (with HbA1c reductions of approximately 0.4%, reported in systematic reviews with meta-analysis). However, further studies are needed to determine the optimal periodontal care to achieve and sustain better glycaemic control as well as to determine if prevention or treatment of periodontitis will result in the reduction of diabetes complications, such as cardiovascular and renal diseases.

CONCLUSIONS

PERIODONTAL HEALTH IS A CRUCIAL COMPONENT of general health, particularly in subjects with diabetes. For that reason, periodontal assessment and management are crucial in this population. People with DM should be aware of their increased risk for periodontitis as well as the negative impact of this condition upon their glycemic control. Dental professionals have an important role not just in the periodontal treatment of people with DM but also helping to identify patients at high risk of developing this disorder.

IMPLICATIONS FOR ACTION

FOR DENTISTS

Patients with DM have several direct implications for the dental professional, as (1) they are at a higher risk of suffering periodontitis, particularly if poorly controlled; (2) they may improve their glycaemic control after successful periodontal therapy; (3) they are at risk of hypoglaecemic episodes while attending the dental surgery; and (4) people with undiagnosed DM attending the dental surgery could have an opportunity for being screened and identified as having a high risk of suffering diabetes, leading to an earlier diagnosis.

FOR MEDICAL DOCTORS

Physicians and other medical health professionals should be aware that periodontitis risk is increased by DM, and that patients with both DM and periodontitis could have a greater difficulty in achieving glycemic control and are at higher risk for diabetic complications, such as cardiovascular and kidney disease. For these reasons, patients with type 1, 2 or gestational diabetes should receive a thorough oral examination, including comprehensive periodontal examination. Patients with DM should be placed on a preventive care regime and monitored regularly (at least annually) for periodontal changes; for children and adolescents annual oral screening should ideally start at 6 years.

FOR THE GENERAL POPULATION

People with DM should receive oral-health education and understand their increased risk for periodontitis and the importance of keeping healthy gums in order to control DM. Like DM, periodontitis is a chronic condition that requires life-long maintenance and regular dental check-ups. Even if no symptom is present, patients with DM should follow a regular recall programme in order to identify early signs of gum disease. For those who do not suffer from DM but present some risk factors, including periodontitis, it is important to get a medical check-up to identify potential undiagnosed hyperglycaemia.

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PERIODONTITIS AND CARDIOVASCULAR DISEASES.

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ABSTRACT

Background

Periodontitis (PD) and Cardiovascular Diseases (CVD) are chronic inflammatory disorders amongst the most common non-communicable diseases. Observational studies confirm a moderate but consistent association between PD and CVD. Patients suffering from PD have an increased future risk of CVD [mainly stroke and myocardial infarction (MI)]. A number of plausible mechanisms have been investigated including bacterial dissemination, systemic inflammation and microbiome changes. The aim of this review was to evaluate the available evidence on the systemic benefits of achieving/maintaining periodontal health in terms of future CVD.

Methods

This is a narrative review on the association between PD and CVD. A literature search of intervention and observational studies in English language was performed in MEDLINE, OVID and Cochrane Oral Health Group's Trial Register database up to December 2016, limited to the following terms "cardiovascular diseases", "myocardial infarction", "coronary heart disease", "periodontal", "periodontitis", "treatment", "clinical trial", "systematic review", "meta-analysis". In addition, references cited in reviewed studies were evaluated for relevant manuscripts.

Results

The search confirmed a consistent association between the two diseases with an average 15% increased risk of CVD in patients suffering from PD. No evidence, however, was available of the impact of restoring periodontal health on CVD hard outcomes such as stroke or myocardial infarction. Some evidence was found on the effects of periodontal therapy on subclinical atherosclerosis whilst moderate evidence suggested a positive effect on the endothelial function and systemic inflammation.

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Conclusions
The current evidence supports the association between PD and CVD. A beneficial effect of periodontal treatment on cardiovascular health has been demonstrated via surrogate markers. Further larger and longer follow-up studies are necessary to validate these benefit on CVD events as to confirm a causal association between the two diseases.

INTRODUCTION

CARDIOVASCULAR DISEASES (CVD) represent a group of non-communicable conditions, affecting primarily the heart and blood vessels, including coronary heart disease, stroke, congestive heart failure, and peripheral artery disease. CVD are the most common cause of death worldwide, with the 2013 Global Burden of Disease study estimating that 17.3 million deaths globally are related to CVD (Moran et al. 2014). Approximately 31% of all deaths and 45% of all non-communicable disease deaths are due to CVD, more than twice those caused by cancer. CVD accounts for 45% of all deaths in Europe (European Heart Network 2017). Despite a global decrease in CVD mortality, in Europe more than 4 million people die from CVD every year, with more than 1.4 million dying prematurely, before the age of 75 years. The overall cost of CVD within Europe is estimated to be €210 billion a year. Of the total cost, around 53% (€111 billion) is due to health care costs, 26% (€54 billion) to productivity losses and 21% (€45 billion) to the informal care of people suffering from CVD.

Seminal epidemiological work, such as the Framingham Study, helped identify the classical risk factors for CVD including: male sex, increasing age, family history, smoking habit, presence of diabetes, obesity, hypertension, hyperlipidemia and a sedentary lifestyle (O'Donnell & Elosua 2008).

CVD are mainly due to atherosclerosis consisting in the thickening of the blood vessel wall due the accumulation of lipids and fibrous components forming plaques. Excluding the non-modifiable factors, including age, sex and family history – management of atherosclerosis is achieved by controlling its main risk factors such as smoking, diabetes, hyperlipidemia, adiposity, and blood pressure. These established risk factors are believed to account for somewhere in the region of 70-90% of incident coronary heart diseases cases (Stone et al. 2014). However, preventive campaigns dedicated to the control of all recognized risk factors have not be sufficient in reducing the impact of CVDs on the health of the general population.

Emerging CVDs risk factors have nevertheless been identified. Inflammation contributes to the development of atheroma formation and to its rupture leading to the development of clinical events. Epidemiological studies have investigated the impact of various infectious agents on systemic inflammation and autoimmunity suggesting an increased risk and progression of CVDs.

Periodontitis (PD) is a chronic inflammatory disease, and it has been considered the 6th most common non-communicable disease by the World Health Organization (Marcenes et al. 2013). The disease is characterized by local gingival inflammation, which if left untreated would eventually result in bone and tooth loss. PD is also linked to systemic inflammation and a chronic host response, which might represent the missing link with other systemic health outcomes (i.e. CVD or diabetes complications).

Table 1. Classic risk factors for CVDs.

Non-Modifiable	**Age, Gender, Familiarity**
Modifiable	**Smoking, blood pressure, diabetes, sedentary lifestyle, adiposity, high cholesterol**

Biological plausibility: explanation of the proposed mechanisms of association

Multiple plausible mechanisms have been suggested in support of a causal link between PD and CVD. Periodontal inflammation results in the formation of gum pockets, which present with an ulcerated and permeable epithelial lining. This allows putative pathogens and/or their byproducts gaining access to the circulation and trigger a systemic inflammatory response involving the endothelium and immune cells (Figure 1) (Reyes et al. 2013, Schenkein & Loos 2013). Bacterial DNA has been identified not only in carotid artery specimens but also at other distant locations confirming the ability of pathogens to invade the endothelial barrier and trigger a local response. Bacteria can also trigger a prothrombotic state but affecting platelet function or travelling into host cells (i.e. dendritic cells) disseminate at distant sites activating local inflammatory processes.

A systemic inflammatory response, triggered by the local infectious/inflammatory pathways, has been implicated on the onset and progression of vascular diseases. An immune response to common periodontal pathogens has been reported but, rather than being protective, this response might also target host cells and promote endothelial dysfunction (the early step for atherogenesis). A number of experimental and clinical studies have been reported and confirming that these mechanisms are biologically plausible.

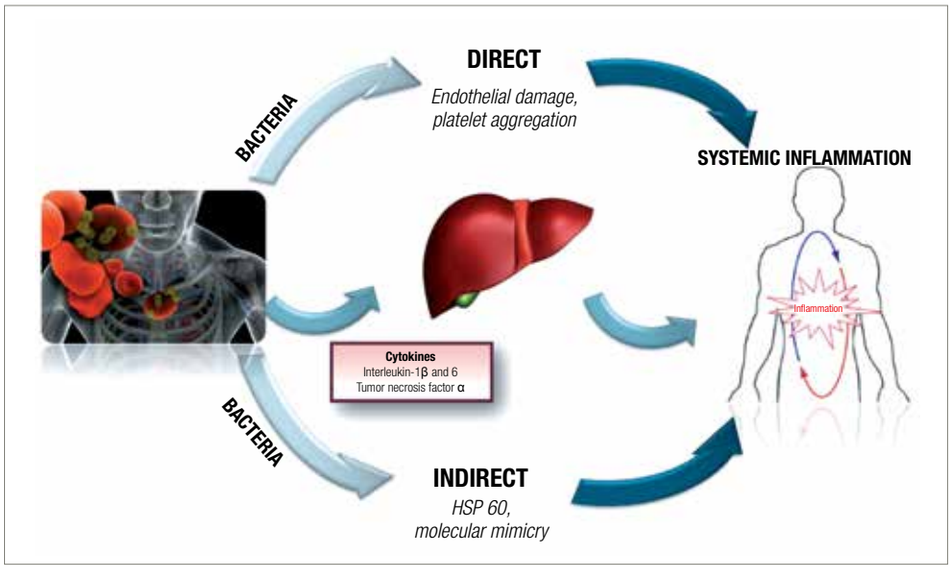

Figure 1.
Plausible mechanisms linking periodontitis and cardiovascular diseases.

An alternative novel mechanistic pathway has emerged recently. Due to the discovery of the interplay between the gut microbiome and systemic inflammation (mainly due to endotoxin release), recent experiments on mice reported that *Porphyromonas gingivalis* can cause alterations to the gut microbiota, leading to indirect induction of systemic inflammation. Ingestion of oral pathogens and colonization of the gut flora could be an important phenomenon in patients with periodontitis. In addition, the dissemination of bacterial metabolites either because ingested or dumped into the systemic circulation could directly affect the endothelium and vascular function (Arimatsu et al. 2014).

Epidemiological evidence: summary of the most relevant results

The link between poor oral health and CVDs was reported for the first time in 1983, when a cardiologist completed an observational study analyzing the oral-health status of 211 patients who suffered from a myocardial infarction (MI) and compared them to 366 controls. A lower level of periodontal health was reported in the test group and the diagnosis of poor periodontal and dental health was strongly associated with the risk of MI (Mattila et al. 1989). Almost 30 years later, a larger case-control study was performed in Sweden comparing the periodontal status of about 800 patients with MI and an almost equal number of controls. The PAROKRANK study confirmed the original report that diagnosis of periodontitis is linked to a 30% increased risk of MI, independent of the traditional CVD factors (Ryden et al. 2016). Epidemiological evidence from multiple observational trials has linked PD to cardiovascular events. However not all observational data supports this association.

Individuals with PD, on average present with a 15% greater risk of developing future CVD. A number of systematic reviews have confirmed this association (Figure 2) (Dietrich et al. 2017).

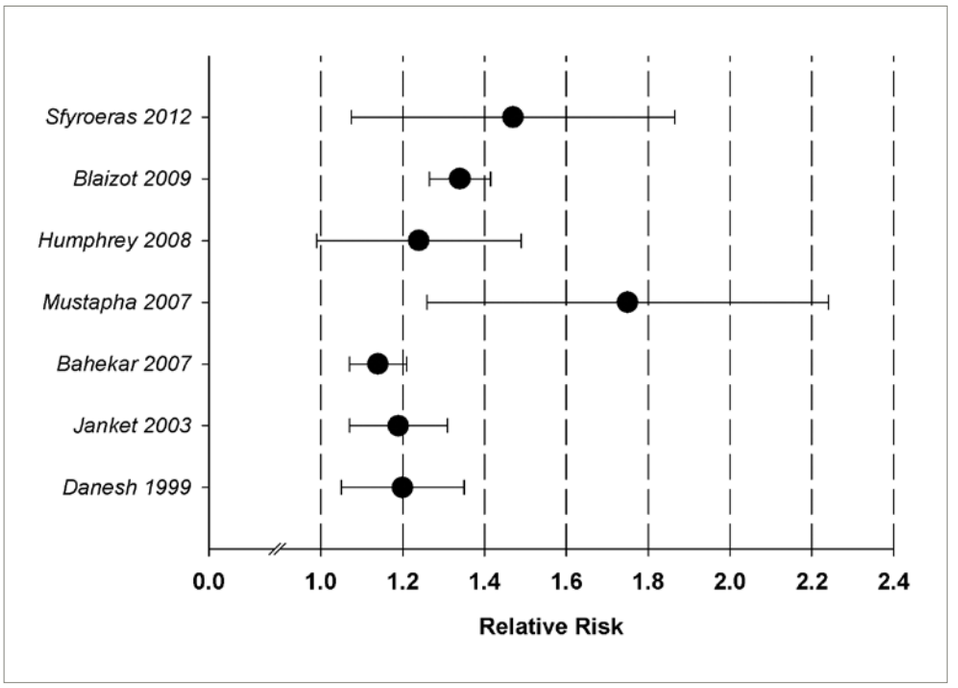

Figure 2.
Systematic reviews estimated relative risk of cardiovascular diseases in patients with periodontitis.

A recent cohort study report on CVD among 1,400 men aged between 60 to 70 years, showed that severe loss of periodontal attachment doubled the risk of death when compared with controls (15.7% versus 7.9%). Furthermore, a meta-analysis of observational studies assessing the relationship between PD and total CVD reported that patients with periodontitis had a 15% increased risk of future CVD when compared to healthy individuals (Linden et al. 2012). Both the American Heart Association (AHA) and the American Academy of Periodontology and the European Federation of Periodontology (AAP/EFP Symposium) reviewed the evidence underpinning these associations and concluded that PD is associated with atherosclerosis independently of known confounders (Tonetti & Van Dyke 2013).

Proposed benefits of periodontal health/treatment on CVD outcomes

To date, only two clinical studies have investigated the effect of periodontal treatment on the primary or secondary prevention of cardiovascular events, such as MI or stroke, reporting no evidence for a beneficial effect of periodontal interventions on hard cardiovascular outcomes. As recently concluded by the AHA and EFP/AAP position papers, on the association between PD and CVD outcomes, no evidence can be found either in favour or against it (D'Aiuto et al. 2013).

There is, however, moderate evidence on the beneficial effects of periodontal treatment on surrogate and novel CVD outcomes such as endothelial function, subclinical atherosclerosis assessed by intima-media thickness of the common carotid artery (c-IMT) and systemic inflammation (Orlandi et al. 2014).

Reduced endothelial function and a thicker c-IMT are linked to increased future risk of CVD risk. A recent meta-analysis confirmed that diagnosis of PD is consistently associated with impaired endothelial function (stiffer arteries) and further periodontal treatment improved this early measure of atherosclerosis (Orlandi et al. 2014). The largest randomized trial published, included 120 patients with severe and generalized PD but no other systemic diseases. The results of the study confirmed an improvement of at least 1% in endothelial function 6 months after periodontal treatment (consisting of a single session of non-surgical periodontal therapy and locally delivered antibiotics) (Tonetti et al. 2007). Two more intervention trials were reported on the effects of periodontal therapy on c-IMT changes. One cohort study reported a reduction of c-IMT after 12 months of periodontal therapy but no control group and limited information on the vascular assessments are the major limitations (Piconi et al. 2009). The other study was performed in Australia including 168 Aboriginal participants suffering from PD and reporting a decrease in c-IMT after 12 months of a single session of non-surgical periodontal therapy in the test group but not in the control group. The difference in c-IMT between the two study groups at 12 months was statistically significant (0.026 mm) (Skilton et al. 2011). These results are promising although a number of limitations were observed in the study, including the lack of supportive periodontal therapy and a substandard protocol of vascular measurements, which could have affected the results.

Further, the clinical relevance of such a small difference in mm is debatable. Whilst observational evidence suggests that each 0.03-mm increase per year in c-IMT confers a doubled relative risk for future nonfatal MI or CVD death (Hodis et al. 1998), the results of the studies on periodontal treatment and c-IMT have to be interpreted with great caution.

Lastly, when appraising the published evidence on novel CVD risk markers including inflammation, a good number of intervention trials have been reported on a variety of serum biomarkers. Based on the evidence examined, there is inconclusive evidence of a potential benefit of performing periodontal therapy in reducing leucocytes counts, lipid fractions, fibrinogen, serum amyloid A, tumour necrosis factor (TNF)-α and other Interleukins (Orlandi et al. 2014). On the contrary, there is moderate evidence confirming that periodontal treatment reduces systemic inflammation as assessed by serum C-reactive protein (CRP) levels and in some extent by Interleukin-6 (Orlandi et al. 2014, Freitas et al. 2012). There is also sufficient evidence to suggest that periodontal treatment (non-surgical periodontal therapy) triggers an acute inflammatory response with vascular implications and this perturbation lasts up to 1 month after the initial therapy session (D'Aiuto et al. 2013). Little comparative evidence was found on the role of periodontal therapy on biomarkers of oxidative stress whilst the available evidence suggests a possible reduction of these biomarkers in the medium term.

SUMMARY

AFTER MORE THAN 30 YEARS from the first reports on the association between dental infections/periodontitis and CVD outcomes, we are still debating whether these associations are causal or casual in nature. Over the last 10 years, the number of clinical intervention trials has multiplied including both traditional and novel CVD outcomes in response to periodontal therapy. However, after a critical appraisal of the evidence reported to date, we confirm that there is still minimal or insufficient comparative evidence on the effect of periodontal therapy on CVD outcomes and or subclinical atherosclerosis. A number of clinical trials have helped our understanding of the potential systemic implications of periodontal therapy. Indeed, the treatment is associated with a robust acute host response and a delayed reduction of chronic inflammation. Whilst the systemic implications of the acute effects are not fully understood at this time, the progressive reduction/improvement in traditional and novel CVD factors raises an important question: should periodontal assessment and therapy be included in the management of CVD risk? Firstly the majority of clinical trials assessed was of limited sample size (<500) and the length of follow-up limited only up to 6-12 months. This represents perhaps the most important limitation in interpreting the data. Both PD and CVD represent long-term chronic conditions. In particular, atheroma formation has been identified very early in life (i.e. already in young children). We could speculate therefore that performing some periodontal treatment only at the end of atheroma evolution (much later in life) might not represent an effective method of preventing further progression of the disease nor the occurrence of acute vascular events. Further research efforts should be devoted in designed appropriate clinical trials on the delivery of effective oral health promotion early in life and monitor the potential beneficial effects on systemic health much later in life. Further, the multifactorial aetiology of both PD and CVD and the fact that both share a common inflammatory nature would indicate that the mere control/removal of local gingival infection might not be sufficient in producing a systemic sustained benefit. In turn additional therapeutic approaches should be researched including host modulation therapies in combination with standard periodontal therapy. These novel approaches at this time have not been fully tested also because of the limited knowledge of the mechanisms involved in the onset and progression of both PD and CVD. The only consistent beneficial effect of periodontal therapy was found on measures of endothelial function that represents a surrogate marker of CVD. Whilst endothelial dysfunction is predictive of future CVD risk/outcomes, it does not, however, represent an efficient research outcome to be implemented in large-scale intervention trials.

CONCLUSIONS

THE CURRENT LEVEL and amount of evidence supports a moderate but consistent association between PD and CVD. A beneficial effect of periodontal treatment on cardiovascular health can be found when surrogate markers of CVD are adopted. Further larger and longer follow-up studies are necessary to validate these benefits on CVD events and to confirm a causal association between the two diseases.

IMPLICATIONS FOR ACTION

FOR DENTISTS, FOR MEDICAL DOCTORS, FOR THE PUBLIC.
In agreement with the recent recommendations discussed at the joint EFP/AAP Symposium on Systemic Diseases in 2012, the diagnosis and management of PD represent an important public-health matter (Tonetti & Van Dyke 2013).

Firstly, PD is the 6th most common disease on the globe with three-quarters of a billion people affected. It is a recognized cause of disability and worsened quality of life. As risk factors for PD are also causing CVD, the WHO Common Risk Factor Approach to improving human health should include self-performed oral hygiene (Sheiham 1992).

Secondly, as a chronic inflammatory disease PD could have potentially negative consequences for general health. In particular, a diagnosis of PD may contribute to CVD risk stratification. Further evidence is required to confirm a beneficial effect of achieving periodontal health over and above currently established lifestyle and drug-based treatment models for CVD.

General Medical and Dental practitioners should be aware of the evidence that links PD to CVD, advising patients of the potential risks. However the main role of the clinicians remains oral-health promotion for the benefit of the public in order to reduce the impact of complications and tooth loss on patients' quality of life. Patients suffering from PD and presenting with other risk factors for CVD should be referred to a physician if they have not received an assessment within the last year. All modifiable lifestyle-associated risk factors for periodontitis (and CVD) should be addressed in the dental surgery including smoking-cessation programs and advice on lifestyle modifications (diet and exercise). This may be better achieved in collaboration with other specialists.

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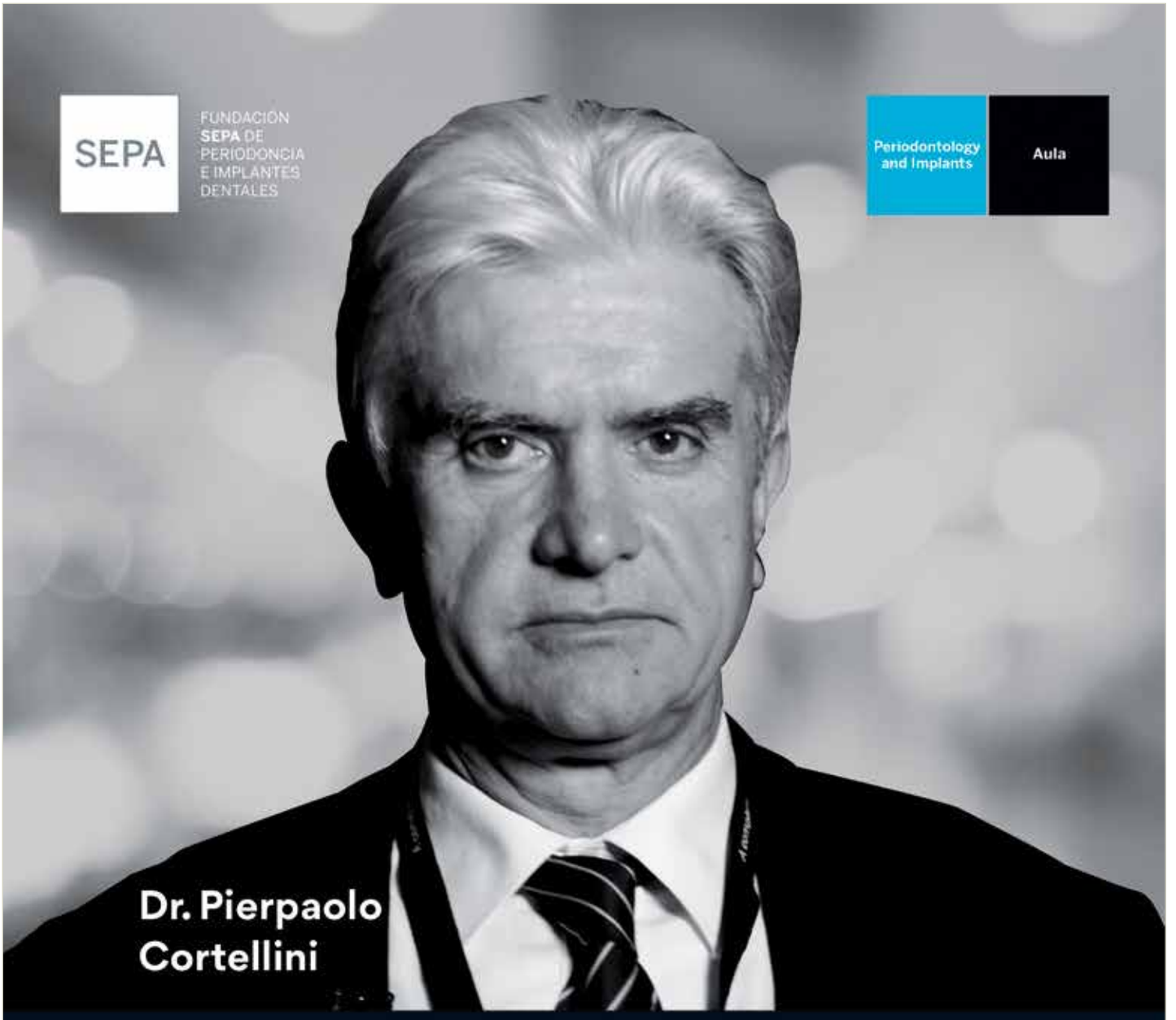

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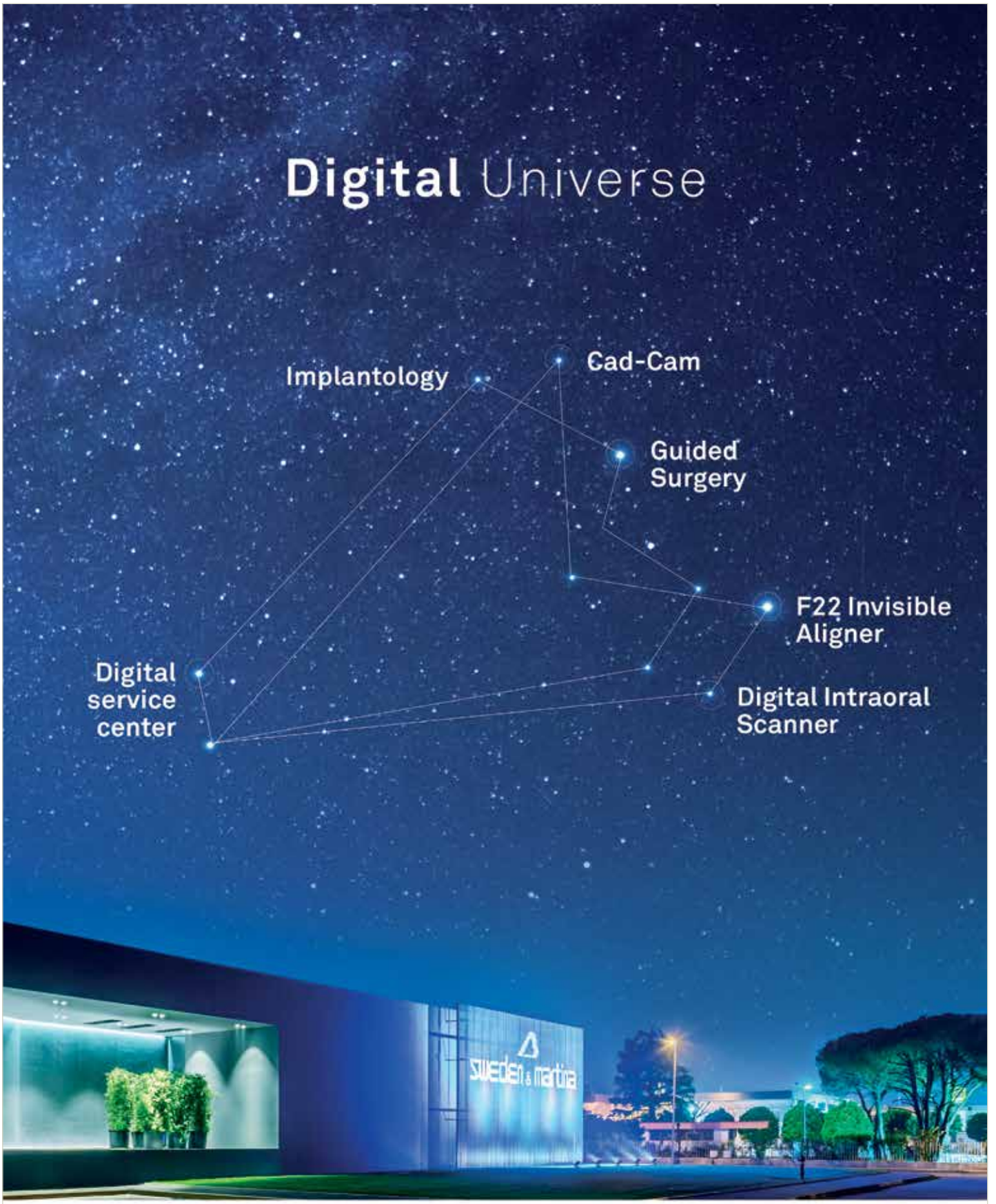

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THE LINK BETWEEN PERIODONTITIS AND ERECTILE DYSFUNCTION (VASCULOGENIC IMPOTENCE).

BRUNO G. LOOS.

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ABSTRACT

PERIODONTITIS HAS BEEN ASSOCIATED with atherosclerotic cardiovascular diseases (ACVD). Based on longitudinal studies in large cohorts it has been shown that periodontitis can be regarded as another risk factor for the sequalae of ACVD such as myocardial infarction, cerebrovascular accidents and death. Atherosclerotic pathology lays at the basis of ACVD events and periodontitis can exacerbate the atherogenic process. With this knowledge, it seems highly conceivable that periodontitis is also associated with erectile dysfunction (ED; vasculogenic impotence). Currently ED is mainly considered as another complication of atherosclerotic changes in the vascular system. Nine studies have investigated the relationship of ED with periodontitis and all found an association. One meta-analysis, including 4 eligible (out total of 9) studies reported a significant odds ratio (OR) of 3 [95% confidence interval (CI) 1.87 - 5.05, p <0.001] for the association. However, there was considerable heterogeneity among the 4 studies. Moreover, one short-term-treatment study indicated that periodontal intervention can decrease ED complaints as measured by questionnaires. These preliminary positive results can also be included in the motivation of dental professionals and male patients; periodontitis screening and, if indicated, periodontal treatment, seem helpful to manage this form of impotence.

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INTRODUCTION

IN THE LAST 25 YEARS, periodontitis has been associated with multiple systemic diseases (Chapple & Genco 2013, Sanz & Korman 2013, Linden et al. 2013, Tonetti & Van Dyke 2013, Gulati et al. 2013). For some systemic diseases the relationship with periodontitis has moved from association to risk factor. Thus, periodontitis is now proposed as risk factor for atherosclerotic cardiovascular diseases (ACVD), lung infections, premature and dysmature birth and other pregnancy complications, rheumatoid arthritis (RA), and diabetes, in particular diabetes mellitus type 2. But beyond these often-studied diseases in relation to periodontitis, more medical conditions seem to have a link with periodontitis. Recently, Monsarrat et al. (2016) have explored clinical-trial databases and concluded, from their extensive bio-informatic efforts, that currently in the world, periodontitis is researched in relation to 57 distinct and unique systemic conditions, based on Medical Subheadings (Mesh) terms. Nevertheless, it needs to be acknowledged that periodontal diseases are not yet proven to be associated with all of these 57 unique conditions and/or diseases, but that they are currently being investigated to see how possible relationships may be explained and could initiate or contribute to the severity of periodontitis (Loos 2016). The links between periodontitis and other systemic diseases may also be studied by periodontal intervention studies; treatment of periodontitis may or may not alleviate the symptoms, progression or severity of the disease.

Periodontitis and ACVD

The second most investigated link of periodontitis with a systemic disease is its association with ACVD (the link betweem periodontal diseases and diabetes is the most researched). Traditionally, in studies, we define ACVD as proven forms of atherosclerosis, and ACVD events and/or conditions are angina pectoris, myocardial infarction (heart attack), a cerebrovascular accident (CVA, stroke), peripheral artery disease or death due to fatal heart attack or stroke. Today, it is widely accepted that the most common cause of erectile dysfunction (ED) is also a complication of atherosclerotic vascular pathology, hence it is known as vasculogenic impotence (Figure 1). These outcome measures of ACVD can be studied in relationship to chronic inflammatory diseases such as periodontitis.

In all, the link between periodontitis and ACVD is now beyond doubt. The editors of the *Journal of the American Heart Association* and of the *Journal of Periodontology* have jointly concluded that the relationship between these two diseases truly exists (Friedewald et al. 2009). Also, more recently, at the Workshop on Periodontal Diseases and Systemic Diseases jointly organized by the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP), it was once again concluded that both diseases can co-occur and that periodontitis could be a risk factor for ACVD (Tonetti & Van Dyke 2013). Moreover, several mechanistic links have been proposed as to how periodontitis may be "causally" related to ACVD and/or atherosclerotic lesions (Schenkein & Loos 2013). Longitudinal studies generally indicate that having periodontitis at the start of the study, increases the risk of suffering from an ACVD event [myocardial infraction (MI), cerebrovascular accident (CVA), death] with at least fifty percent (relative risk 1.5) (Humphrey et al. 2008). For males <60 years of age, this risk increases 2-fold over one's "normal" risk (Dietrich et al. 2008).

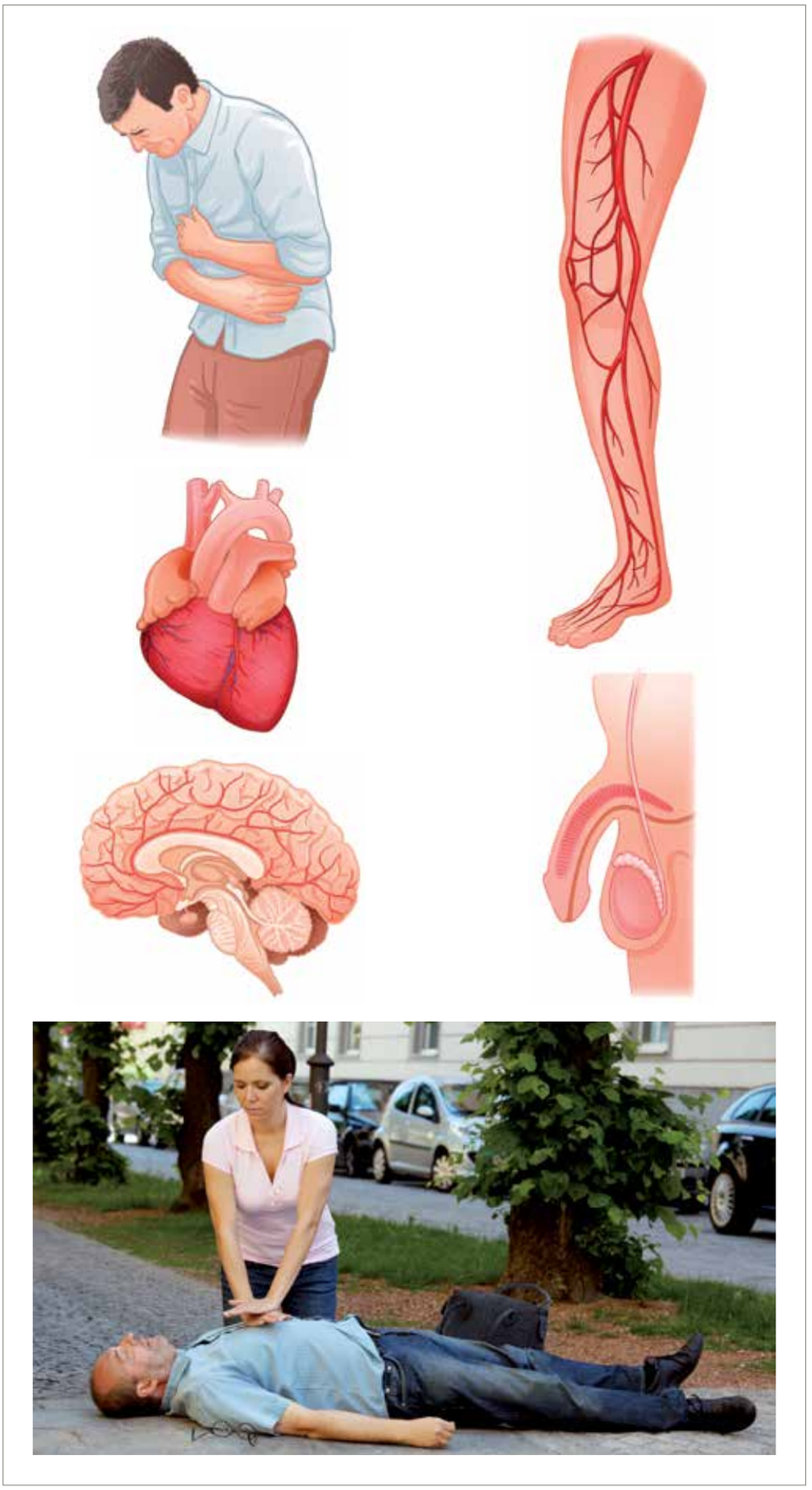

Figure 1.
Most common sequellae of atherosclerotic (cardio)vascular disease: Angina pectoris; Myocardial infarct (heart attack); Cerebrovascular accident (stroke); Peripheral artery disease; Sudden Cardiac Death; Erectile dysfunction (vasculogenic impotence).

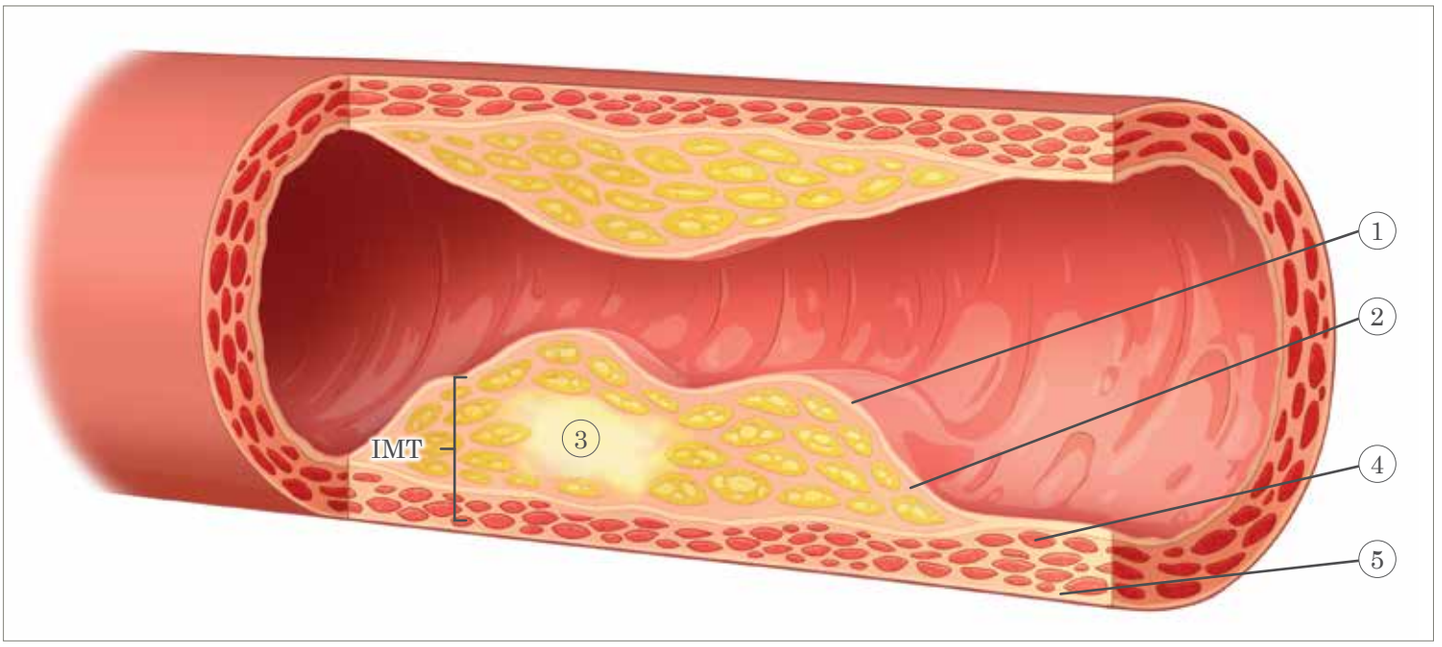

Figure 2.
An artist's drawing of an atherosclerotic artery; 1. Endothelial lining; 2. Inflammatory infiltrate; 3. Calcifications; 4. Connective tissue; 5. Muscle layer. The structures 1 to 4 can be visualized by ultrasound and measured as the IMT (Intima Media Thickness) (Schenkein & Loos 2013).

The underlying cause of ACVD is atherogenesis and endothelial dysfunction. This is the result of formation of atherosclerotic plaques in the large and small arteria (Figure 2). In general, due to the chronic process of atherogenesis, arteries, even the largest of all (the aorta), become less elastic, more stiff and the intima media wall increases in thickness. In predilection places, thicker atherosclerotic plaques become apparent; often in the carotid arteries around the bifurcations of the common carotid artery towards the arteria *carotis interna* and *externa*. But also coronary arteries are the most well-known places for the dangerous formation of atherosclerotic plaques.

Indeed, many cross-sectional clinical studies have found that periodontitis is strongly related to these above parameters of atherosclerosis. Using different tools and measures, periodontitis is associated with thickened intima media in carotid arteries, with reduced elasticity and dilatory capacities of the brachial arteries, and with general stiffening of the major descending aorta and brachial arteries. In addition to association studies, intervention studies have investigated how periodontal treatment can improve the cardiovascular system. In other words, whether periodontal therapy can affect the above parameters. Overall, all periodontal-intervention studies indicate that periodontitis treatment does improve the condition of the vascular system. Interestingly, mostly from 6 months postoperatively, we notice in the literature that the thickness of the intima media of carotid arteries is reduced, that the stiffness of the major descending aorta and brachial artery is reduced, and that the elasticity and dilatory capacity of the brachial artery is improved. In conjunction with these clinical improvements of the cardiovascular system after appropriate periodontal therapy, blood plasma markers of ACVD are reduced (Han et al. 2014, Teeuw et al. 2014). We can conclude that periodontal therapy not only improves the prognosis of teeth and improves the oral condition, but also improves the condition of the cardiovascular system. This is a double gain for the patient and should motivate the dental professional and patients to start periodontal therapy in those who need it.

Table 1. Overview of studies investigating a possible association of ED with periodontitis.

	Study	Country of study	Number of subjects in study	Mean age ± standard deviation (range)	ED associated with periodontitis
1	Zadik et al. 2009	Israel	305	40 ± 7	yes
2	Sharma et al. 2011	India	70	35 ± 4	yes
3	Keller et al. 2012	Taiwan	195,336	49 ± 13	yes
4	Eltas et al. 2013	Turkey	120	37 ± 7	yes
5	Oguz et al. 2013	Turkey	162	35 ± 5	yes
6	Uppal et al. 2014	India	53	(25 – 40)	yes
7	Matsumoto et al. 2014	Japan	88	51 ± 17	yes
8	Tsao et al. 2015	Taiwan	15,315	48 ± 13	yes
9	Lee et al. 2015	Korea	551,414	unknown	yes

ED: erectile dysfunction

The link between periodontitis and erectile dysfunction

Among the 57 medical diseases that are currently investigated in relation to periodontitis, is also the condition erectile dysfunction (ED). This is defined as the persistent or recurrent inability to complete or continue a penile erection sufficient for satisfactory sexual performance (American Psychiatric Association 1994, Lauman et al. 1999, Lue et al. 2004, Kellesarian et al. 2016, Wang et al. 2016).

It is now well accepted that this apparent common condition has definitively not (only) a psychiatric background. In fact, it is like so many other common disorders, a multifactorial disease. Nevertheless, it is estimated that about 80% of ED cases are for the greater part, due to an underlying systemic illness; the most common pathophysiological explanation behind ED is atherosclerosis of the vascular system. Therefore, ED is also known as vasculogenic impotence. Epidemiological studies have shown that men with ED most often have a history of ACVD or develop a major ACVD event over some years of follow up. Therefore, as it has been extensively argued above, it is not surprising when ACVD and periodontitis are closely linked, that now some new clinical studies in the periodontal arena, have linked periodontitis with ED.

Two recent systematic reviews and meta-analyses have summarized available cross-sectional studies linking periodontal diseases with ED (Kellesarian et al. 2016, Wang et al. 2016). Nine studies have been identified, being performed in various parts of the world (Table 1). The mean age of the male participants in the different studies varied from 35 to 51 years, and all nine studies found an association between ED and periodontitis. The review from Wang et al. (2016) has a robust systematic approach and identified 4 out of these 9 eligible studies to be included in meta-analyses. These four studies (Zadik et al. 2009, Keller et al. 2012, Oguz et al. 2013, Tsao et al. 2014) included a large number of ED patients and controls (together 38,111 patients and 174,807 controls). The odds ratio (OR) among ED patients to have concomitantly periodontitis was overall 3 times as high as among those without ED (95% confidence interval 1.87-5.05). The high OR suggests a strong association between both diseases, however the wide confidence interval indicates a huge variation among the studies and indeed the reported heterogeneity was very large (almost 100%). In conjunction with the 5 other studies not included in the meta-analyses of Wang et al. (2016), which reported on the association (Table 1), we can conclude that the association between ED and periodontitis is existent, but weakly proven and still open for more well controlled studies.

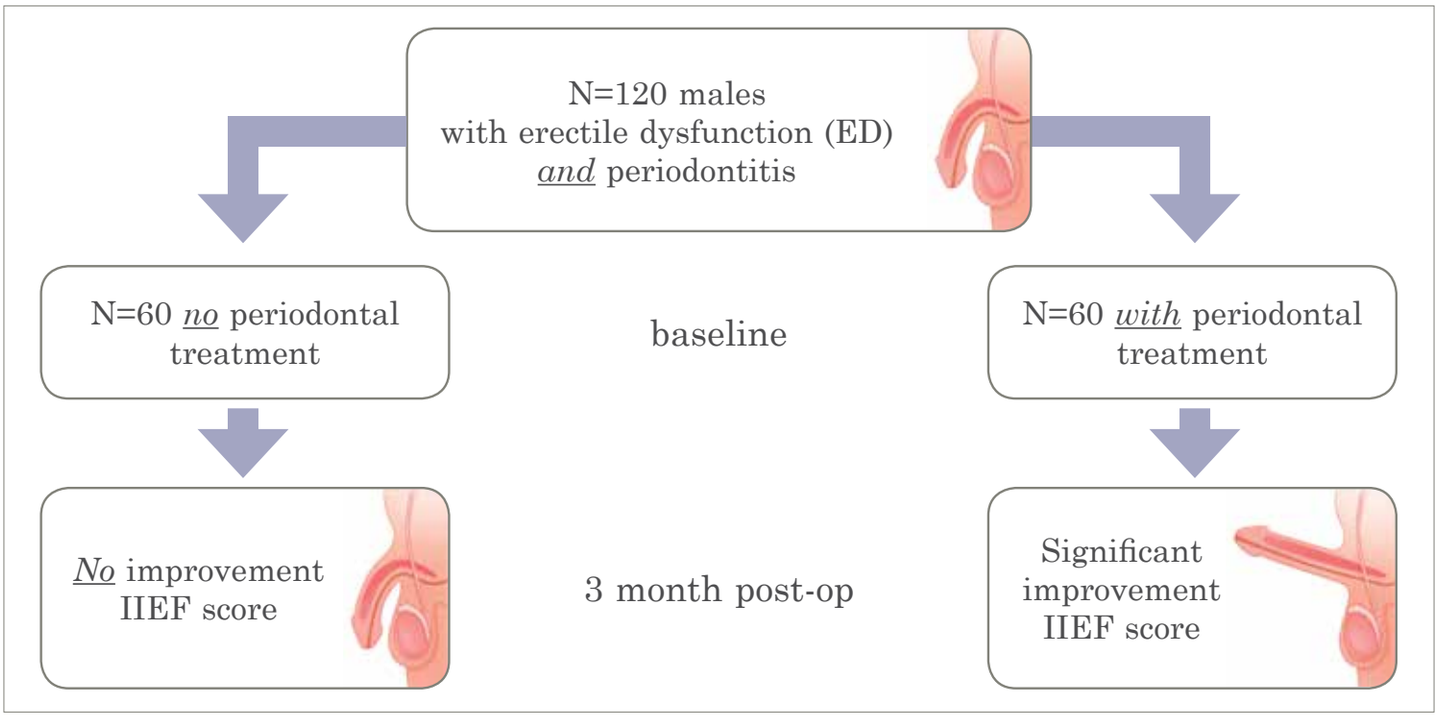

Figure 3.
Effect of periodontal therapy on erectile dysfunction (ED) (Eltas et al. 2013). ED was assessed by scores derived from the questionnaire "International Index of Erectile Dysfunction (IIEF)".

Several issues on the validity of the putative association between ED and periodontitis need to be mentioned. ED is actually measured by validated questionnaires, and no objective measure of ED in the studies has been used. Further, except for the four studies in the systematic review (Wang et al. 2016), some of the other available studies (Table 1) also used questionnaires for the self-diagnosis of periodontitis. Moreover, many covariables may influence the relationship, such as smoking, diabetes, obesity and other lifestyle habits, or other comorbidities. These are currently not fully accounted for.

Despite the above reservations, the association between ED and periodontitis may well be truly existent. Regarding the vast amount of literature on the link between periodontitis and ACVD, it is highly conceivable that periodontitis is also associated with ED, where ED (i.e. vasculogenic impotence) is another complication of a compromised vascular system due to atherosclerosis and concomitant endothelial dysfunction. Therefore, taking this assumption one step further, it would be interesting to know whether periodontal therapy could alleviate ED complaints or reduce scores on the ED questionnaires. After all, many periodontal intervention studies showed improvement of the clinical and biological parameters of ACVD (Han et al. 2014, Teeuw et al. 2014).

One periodontitis-intervention study in ED patients thus far has been performed (Eltas et al. 2013). The study from Eltas et al. was performed in Turkey, set up as a randomized clinical trial (RCT) and involved 120 male participants, who suffered both from ED based on the "International Index of Erectile Dysfunction" score (IIEF questionnaire) and periodontitis (Figure 3). At baseline, 60 men were randomly assigned to "no periodontal treatment" (mean age 36.6 year) and the other half of the study population was assigned to the periodontitis treatment group (mean age 38.1 year). At the 3 months postoperative time point, the periodontally treated males reported significant improvements in their IIEF scores compared to those men in the control group. The study results are encouraging and are the first to show that internists and urologists can also advise their male patients with ED – in addition to checking for ACVD – to visit a dental surgery to check for periodontitis and, if present, to treat this oral inflammatory condition. Periodontal therapy is not the panacea for ED, but could be helpful as part of a complete treatment of vasculogenic impotence. As we have seen for periodontal-treatment studies that can improve the vascular condition as measured by various parameters, it may not be surprising that periodontal treatment could alleviate ED complaints.

CONCLUSIONS

PERIODONTITIS IS ASSOCIATED with various systemic conditions. The link between periodontitis and atherosclerotic cardiovascular diseases is extensively researched and confirmed. In periodontitis patients, the condition of the vascular system is worse compared to non-periodontitis controls employing various parameters such as intima media thickness, flow-mediated dilation and stiffness of the descending and brachial artery. With this knowledge, it is not surprising that periodontitis is also associated with vasculogenic impotence (ED), which condition by and large is also a complication of atherosclerotic changes of arteries and other blood vessels. Nine cross-sectional studies, and a meta-analysis including four of these nine,clear pointing to this link. Moreover, one short-term treatment study indicates that, like the positive effects of periodontal therapy on the named vascular parameters, periodontal intervention can decrease ED complaints as measured by questionnaires. These preliminary positive results can also be included in the motivation of the dental professional and the male patients that periodontitis screening and, if indicated, periodontal treatment, are helpful to manage this form of impotence.

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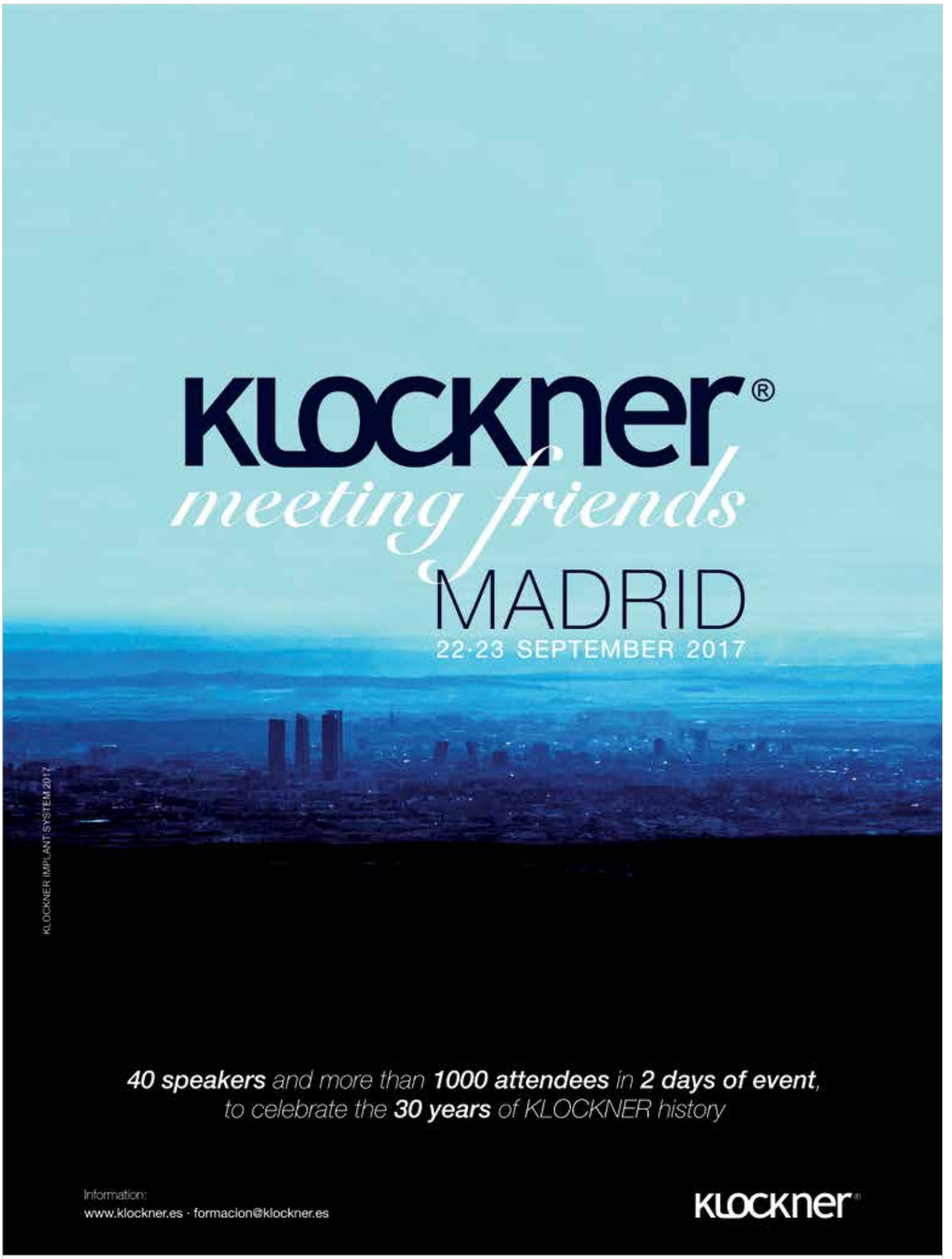

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ABSTRACT

PERIODONTITIS has recently emerged as an important risk factor for the development of Alzheimer's disease later in life. Although there is still much which is not understood about the specific underlying mechanisms, we know that there is a strong association between the two diseases, which relates to the bacteria involved and the chronic inflammatory states that they share. This review examines the evidence for the coexistence of these diseases and the likely reasons as to why periodontitis may trigger a chain of events which finally presents as the most prevalent dementia worldwide.

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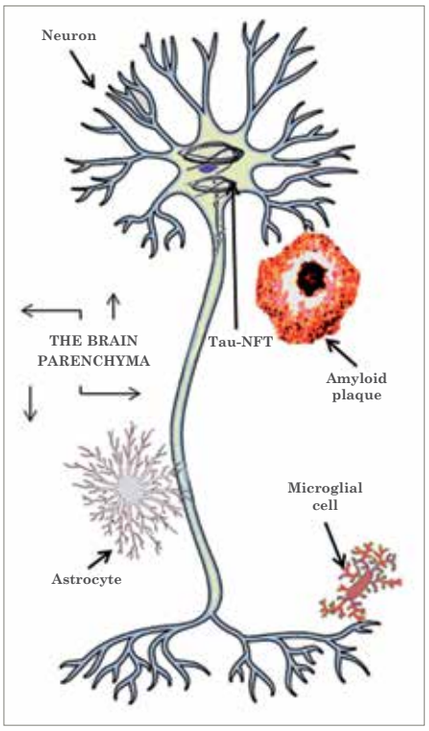

Figure 1.
Schematic model of cell types in the brain parenchyma and the neuropathology associated with Alzheimer's disease.
The two major characteristic markers of pathology in the brain are amyloid plaques and neurofibrillary tangles (NFT). Amyloid plaques are composed mainly of aggregates of the Aβ42 peptide (42 amino acids long), which are deposited outside the neurons in the brain parenchyma, i.e. surrounding tissue. NFT accumulate inside the neurons, and are comprised mainly of peptides from the protein tau, which have an unusually high level of phosphate groups on them. Glial cells are also shown: a microglial cell and an astrocyte, which support the neurons but under certain circumstances can be involved in neuronal damage.

INTRODUCTION

Alzheimer's disease

Statistics and global burden

Alzheimer's disease (AD) is defined by its pathology, largely the presence of abnormal protein deposits, and is a neurodegenerative disease which usually begins with such symptoms as forgetfulness and ends in severe dementia. The pathology can be summarised in Figure 1. AD is the major cause of dementia worldwide (Alzheimer's Disease International 2016) accounting for between 60 and 80% of dementias. Worldwide, currently more than 46 million people are estimated to have dementia and this is expected to rise to 132 million by 2050, with a global cost reaching $US 1trillion in the next two years. As the aging population increases the number of people living with AD is set to rise considerably. Although AD is not necessarily an outcome of aging, its incidence approximately doubles every 5 years from the age of 65 years, and the odds of receiving a diagnosis of AD over 85 years of age exceeds 1:3.

Despite the fact that the disease was first discovered over a hundred years ago (Selzmann: English translation, Alzheimer et al. 1995), the drugs available so far are only able to temporarily reduce the symptoms in some people. However, with new understanding of effects of chronic inflammation and the role of the microbiome, novel possibilities for therapy present themselves.

In the brain, aggregates of Aβ42 peptides are deposited outside the neurons as 'amyloid plaques'. This toxic peptide has destructive effects on nearby neurons, producing reactive oxygen species (ROS) such as hydrogen peroxide, and sticks to many proteins with high affinity including important cell receptors thereby preventing normal function. Aβ42 peptide is produced by most cells including neurons; in AD brain it is spread across the cortical parenchyma and in some subcortical structures. The second characteristic protein aggregation of Alzheimer pathology is that of neurofibrillary tangles (NFT) which are formed inside the neurons. These are composed of peptides cleaved from the protein tau. Tau is a protein which normally enables orderly transport of nutrients and waste in the neurons by stabilising microtubules. This pathology, in general, has a predictable trajectory with the NFT accumulation following a proscribed route in the brain, with areas such as the primary motor region classically being spared. The number of NFT correlates well with the stages of dementia; as do amyloid plaques, although less strongly. The greatest risk factor for AD is age; however, an important factor which has been focussed on more recently is that the underlying pathology is likely to be progressing from 15 to 20 years before diagnosis.

Symptoms

The symptoms of the disease can be attributed to the specific areas of the brain affected. The first noticeable symptoms are forgetfulness, attributable to regions such as the hippocampus, and also hyposmia or anosmia, a reduction or loss of sense of smell. Other neuropsychiatric problems include loss of spatial awareness or language function. Neuropsychiatric changes include depression, aggression, wandering and hallucinations. The final stages involve an inability to perform activities of daily living such as washing and feeding. Death usually occurs 8 to 12 years after diagnosis.

A timeline of disease progression

If we consider generally the changes from before the onset of disease up to late stage, a theoretical schematic may look like Figure 2.

This relates to changes seen in familial cases of AD and so we cannot be sure that this faithfully reflects changes in sporadic AD, although it does seem to reflect post-mortem findings at different stages of the sporadic form of AD. The data are from a prospective, longitudinal study of 128 cases with familial autosomal dominant AD (Bateman et al. 2012) in which assessments of cognition, imaging, blood and cerebrospinal fluid (CSF) levels of tau and Aβ42 were obtained. These data indicate that Aβ42 deposition, and a reduction in glucose uptake into cells, was seen many years before the expected onset of symptoms. These and other data, which focus on the presumed trigger events, such as amyloid and NFT build-up, seem to suggest that efforts should be concentrated on treating patients early, if possible, before any symptoms. This has been borne out by the lack of success in treatments so far. This narrows our options. One possibility is to test for non-intrusive markers of pathology for everyone, preferably in those less than 60 years of age, or another to 'treat' everyone regardless, such as currently occurs with vaccines for measles. However, especially in the face of the prevailing financial climate, a third option of prevention seems commendable. A number of studies have shown that AD is amenable to lifestyle changes and may relate to poor oral health. Stabilization of active periodontal disease and subsequent reduction in oral pathogen load, may possibly lead to a large enough reduction in risk of having dementia to prevent its onset.

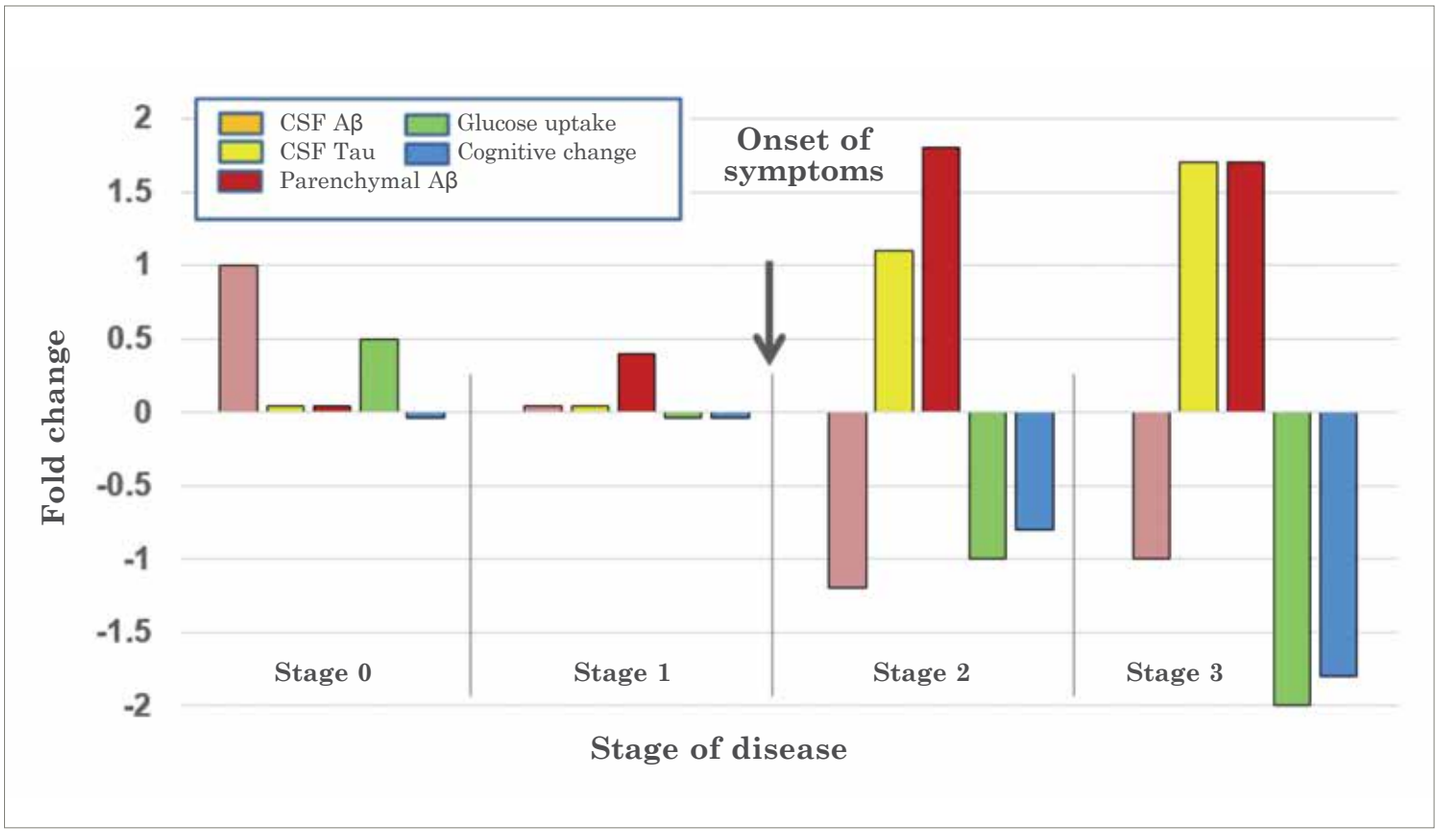

Figure 2.

Changes in brain function from pre-disease to late-stage familial Alzheimer's.

Adapted from Bateman et al. 2012 (Bateman et al. 2012) Longitudinal data, from before onset of symptoms, obtained from people with known AD dominant mutations. This bar chart shows reductions in Aβ42 (orange bars) in cerebrospinal fluid (CSF) over time, commensurate with increases in parenchymal deposition of Aβ42 (red bars) (measured by positron-emission tomography with Pittsburgh compound B [PIB] which binds amyloid) into plaques; a reduced glucose uptake (green bars; measured by fluorodeoxyglucose [FDG]), and an increase in tau into the CSF (yellow bars) which is probably related to disintegration of the neurons. Stage 0 is before the start of the neuropathological process, stage 1 relates to data at 20 years before symptoms, stage 2 is at onset of symptoms and stage 3 is 10 years after diagnosis.

Age, inflammation and the adaptive and innate immune systems

Many studies have shown it is possible to have numerous amyloid plaques in the brain without cognitive decline (Price & Morris 1999, Aizenstein et al. 2008, Hulette et al. 1998, Katzman et al. 1988, Esparza et al. 2013). Rather than assuming these people all to be 'pre-clinical' we might consider the disease in separate phases such that in an initial stage there may be a trigger causing production of Aβ and tau proteins but later, in a cellular phase, the main driver of pathology becomes inflammation (Karran & De Strooper 2016). If it is the inflammatory changes that stimulate the actual process of neurological damage, bearing in mind that in Figure 2 we see no cognitive damage until after 20 years of Aβ42 deposition in the parenchyma, then reducing the inflammatory drive may slow or prevent cognitive decline. Amyloid (Aβ) production is a part of our normal response to acute injury and it is a possibility that the amyloid plaques present in the brains of non-demented individuals are the result of a successful attempt by the brain to deal with an acute insult from microbial pathogens. If we view the whole disease process in this way, we can begin to think about (i) prevention from an early age and (ii) therapy even after the symptoms have manifested.

There is, in fact, much evidence to show that chronic inflammation is a major driver of AD (Weksler et al. 2005, Heneka et al. 2015, Heppner et al. 2015, Marsh et al. 2016). The sources of sustained inflammation may be manifold; however we have some indications as to the principal promoters. The first of these is age. More than 95% of those with AD are over 65 years; 81% are age 75 or older. Our health depends upon an active immune system to protect us from pathogens. As we age, in many cases the adaptive immune system which deals with pathogens in a controlled and enduring manner gradually weakens (Weksler et al. 2005, Weinberger et al. 2008, Castelo-Branco & Soveral 2014, Simon et al. 2015). This leaves the innate immune system as our principal champion of defence; this is rapid but less controlled and may result in excessive production of cytokines or other anti-bacterials which may also damage neurons. With age then, we become more vulnerable to the effects of any prolonged and excessive response to invading microorganisms or other triggers, not only from the microbes themselves but from our own excessive response to them.

Due to the lack of free movement of antibodies across the blood-brain-barrier (BBB) into the brain, microglial cells are the primary immune cells of the brain and have been identified as being central to inflammatory states in many diseases (Cherry et al. 2014, da Fonseca et al. 2014, Holtman et al. 2015). The microglial phenotype is modified by infection by bacteria or other microbial pathogens, and microglial cells become 'primed' during aging and in pathological inflammatory situations (Holtman et al. 2015). Microglia can exist in an activated classical pro-inflammatory state (M1) and an 'alternatively activated' (M2) supportive, anti-inflammatory state. Enhanced phagocytic activity of microglia is likely to be supportive of a degenerating brain in the short term. However, prolonged or dysregulated microglial activation, especially in the context of additional inflammatory events, may result in impaired phagocytosis with increased release of reactive oxygen species (ROS) or cytokines which may exacerbate neuronal damage (Figure 3).

In the vicinity of bacteria or amyloid plaques, microglia produce antibacterial proteins or cytokines in order to eliminate invading pathogens.

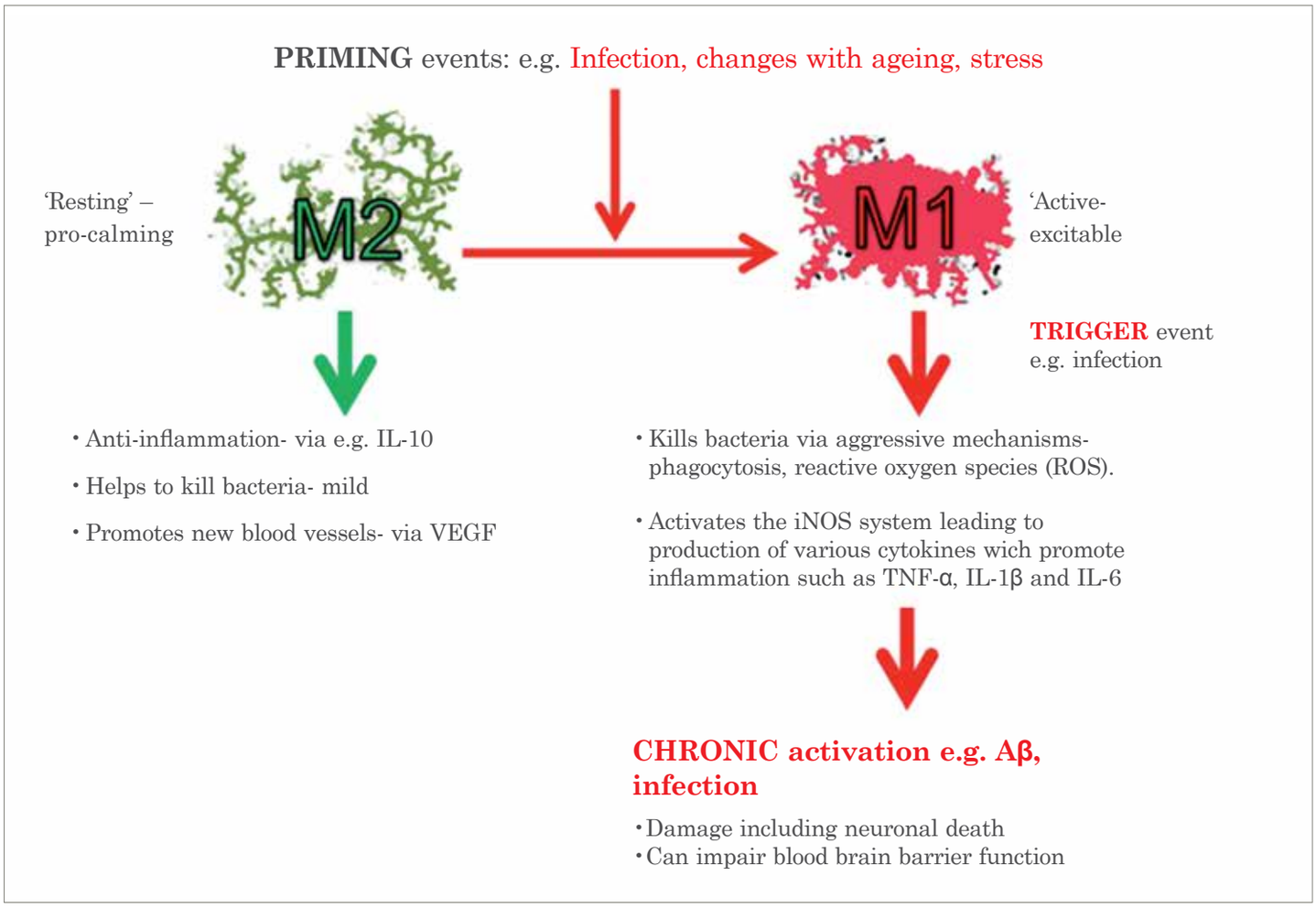

Figure 3.
How microglia may cause chronic inflammation.
Microglial cells are a major part of the brain's immune system, and depending on circumstances move between a so called 'resting' state (M2) and an 'activated' state (M1). Normally the M2 microglia keep the brain in a balanced state, help to control any minor infections, reduce inflammation and also when necessary promote sprouting of blood vessels to help with the flow of nutrients and oxygen. Acute events, such as infection or stress, can alert these cells to change into a more active state. After the event is dealt with they return to a supportive M1 state. However, if provoked chronically, this can lead to a state of hyper-inflammation in which neuronal cell death may occur.

The proposed mechanism of association between periodontitis and Alzheimer's disease.

Following from the understanding that a major driver of AD pathology involves chronic brain inflammation we may ask the question as to how this arises. Recent evidence suggests that Aβ42 itself may be an antibacterial (Soscia et al. 2010, Kamer et al. 2016) and it is probably part of our innate immune system. Therefore Aβ42 may act to kill bacteria, but also its increased production and deposition may result in microglial activation and an upregulation of inflammation which inadvertently sustains a chronic activation of primed microglia which initiates a cycle of inflammatory upregulation. If we assume that one of the possible triggers of chronic inflammation is bacteria, then where does this originate?

From the oral and nasal cavities to the brain

Infections may occur anywhere within the body producing first acute and then chronic infection and inflammation. However, the result of this is usually heat and pain, alerting the host to the site of infection. The mouth is a privileged site in terms of immune response (Novak et al. 2008). Despite the fact that there is a large number and diversity of bacteria within the oral cavity and that the mouth is constantly in contact with allergens, there is not the expected requisite number of inflammatory episodes and this has resulted in the suggestion that the mouth is an immune-tolerant site (Novak et al. 2008). In reality this leads to a situation where llow-level chronic infection, such as periodontitis, may occur over decades without any noticeable level of pain or pyrexia. We therefore suggest that periodontitis provides an ideal driver of inflammation in the brain, able to produce cytokine secretion into the bloodstream, and also situated close enough to the olfactory bulb and tract which allows a direct passage into the cortical parenchyma. The latter would also explain the presence of Alzheimer's pathology in the olfactory bulb (Ohm & Braak 1987, Jellinger & Attems 2005, Franks et al. 2015) which is associated the common early loss of sense of smell which is associated with the progression of pathology (Doty et al. 2003, Doty & Kamath 2014) and with clinical dementia (Attems et al. 2005, Attems & Jellinger 2006) (Figure 4). This has been recognised as a potential marker for diagnosis (Atanasova et al. 2008, Djordjevic et al. 2008). The association between periodontitis and AD is further reviewed (Cerajewska et al. 2015, Shoemark & Allen 2015).

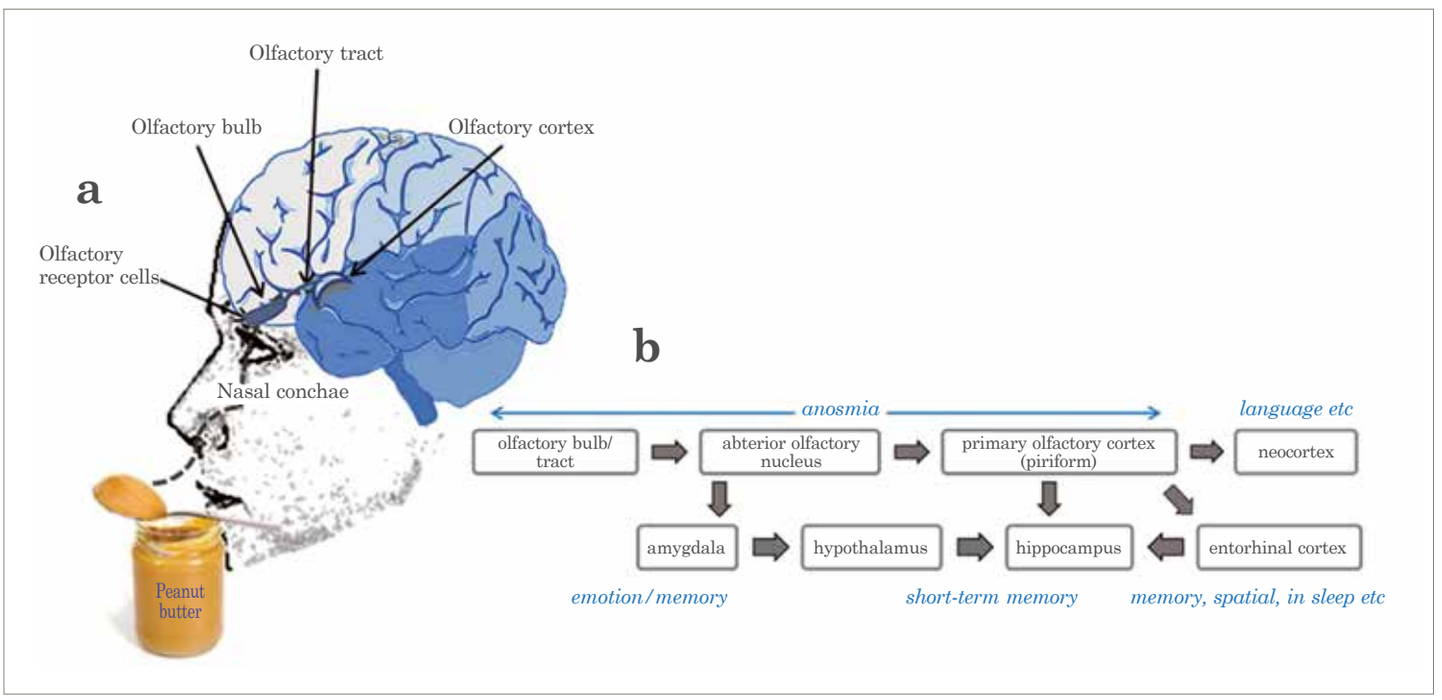

Figure 4.
A pathway from the oral/nasal cavities to the cortical areas of the brain – a possible route by which pathogens may reach the brain.
(Atanasova et al. 2008) The olfactory tract is a likely route for the spread of pathogens such as bacteria and viruses into the brain. Ability to perceive peanut butter may be used as a part of a 'smell test' for diagnosis of AD. (Price & Morris 1999) The systems which are affected, such as the olfactory tract, which contain the classical Alzheimer's pathology.

Evidence: Epidemiology, genetics and scientific research

Epidemiology

A number of epidemiological studies suggest that poor gum health is a risk factor for AD. A study using data from 'The Swedish Twin Registry', in which over 3,000 monozygotic twins were assessed for risks for dementia (Gatz et al. 2006) found it four times more likely that the twin with AD had poorer oral health, and tooth loss before age 35 years, compared with the sibling without dementia. Poor oral health was therefore a significant risk factor. In accord with this, in 2007 a 10-year longitudinal study of dental records of nuns (the Milwaukee Nun Study) of between 75 and 98 years old showed that those with the fewest teeth, lost due to periodontal disease, had the highest risk of dementia (Stein et al. 2007). In 2012, an 18-year longitudinal study of 5,468 normal adults (average 81 years) showed that brushing teeth regularly lowered the risk of AD. Those who did not brush regularly had up to a 65% increased risk of dementia (Paganini-Hill et al. 2012). Recently a small observational study, in which 60 AD patients with and without periodontitis were cognitively assessed and inflammatory markers measured in the blood, showed that after six months there was a sixfold increase in the rate of cognitive decline in those with periodontitis compared to those without (Ide et al. 2016). This would be a remarkable finding and needs to be confirmed by further studies.

Post-mortem studies in Alzheimer brain

Some bacterial infections of the brain, such as seen with bacterial meningitis caused by *Neisseria meningitides*, have severe acute reactions. Other bacteria are able to invade brain tissue without causing such an immediately obvious effect. Diverse bacterial species have been identified in human brain tissue and have been found at higher levels in Alzheimer's brain. Early reports by Judith Miklossy showed obligate oral-based anaerobes such as spirochetes, were present in blood and CSF from Alzheimer's patients but not in age-matched controls (Miklossy 1993) and the literature data for the evidence of oral spirochetes in AD brain has been reviewed with the reported presence of spirochetes in over 90% of AD brains (Miklossy 2011). Additionally, spirochete oral pathogens including *Borrelia burgdorferi* and various Treponemas have been detected at much greater levels than in controls (Riviere et al. 2002, Branton et al. 2013). Recently, Aβ was shown to be a major component of spirochetal biofilms within amyloid plaques in AD brain tissue and it is suggested that bacterial amyloid is a constituent of AD plaques and may contribute to uncontrolled inflammatory drive (Miklossy 2016). Furthermore, elevated plasma levels of antibodies to the oral bacteria *Aggregatibacter actinomycetemcomitans, Tannerella forsythia and Porphyromonas gingivalis* were found in AD patients compared with controls (Kamer et al. 2009). Additionally, in a longitudinal study in cognitively normal people, higher baseline serum antibody levels, specific for the oral anaerobes *Fusobacterium nucleatum* and *Prevotella intermedia*, were shown to correlate a decade later with cognitive deficits (Sparks Stein et al. 2012).

Bacterial infiltration into the brain is likely to result in inflammation and secretion of pro-inflammatory cytokines. For example, TNFα CSF levels in Alzheimer's patients were reported as 25 times that of controls (Tarkowski et al. 1999). Cellular stress and microbial infections elicit inflammatory reactions; in response to this, inflammasomes assemble and a cascade of further secreted cytokines is initiated adding to subsequent pathological processes (Singhrao et al. 2015). The major component of the outer membrane of gram-negative bacteria is lipopolysaccharide (LPS), and LPS from the oral anaerobe P. gingivalis has been detected in the brains of AD patients, but not in control brain tissue (Poole et al. 2013). LPS binds the microglial cell receptor TLR4 and increases inflammation via inflammasome-induced cytokines. Interestingly it has been shown that the TLR4 content in peripheral blood mononuclear cells was increased fourfold in 60 late-onset AD patients as compared to 60 healthy controls with a negative correlation between TLR4 levels and cognitive score (Zhang et al. 2012).

Oral periodontal bacteria implicated in Alzheimer's disease

More than 600 species of oral bacteria have been identified in periodontal pockets. 16S rRNA gene sequences of these bacteria are collected in the Human Oral Microbiome Database (HOMD; www.homd.org) and have been further examined in detail (Chen et al. 2010, Dewhirst et al. 2010). Figure 5 shows some of the most pathogenic of these bacteria and their social groupings.

With periodontitis, a shift in oral population is seen from predominantly aerobic gram positive bacteria such as streptococci to favour gram-negative anaerobic bacteria, usually rods not cocci, including *P. gingivalis, P. intermedia* and *Treponema denticola.* There is evidence that bacterial communities associated with periodontitis are 'inflammo-philic' and are able to use nutrients produced from the breakdown products from gum tissue and bone. In accord with this, anti-inflammatories are able to reduce the bacterial load and prevent loss of bone (Hajishengallis & Sahingur 2014).

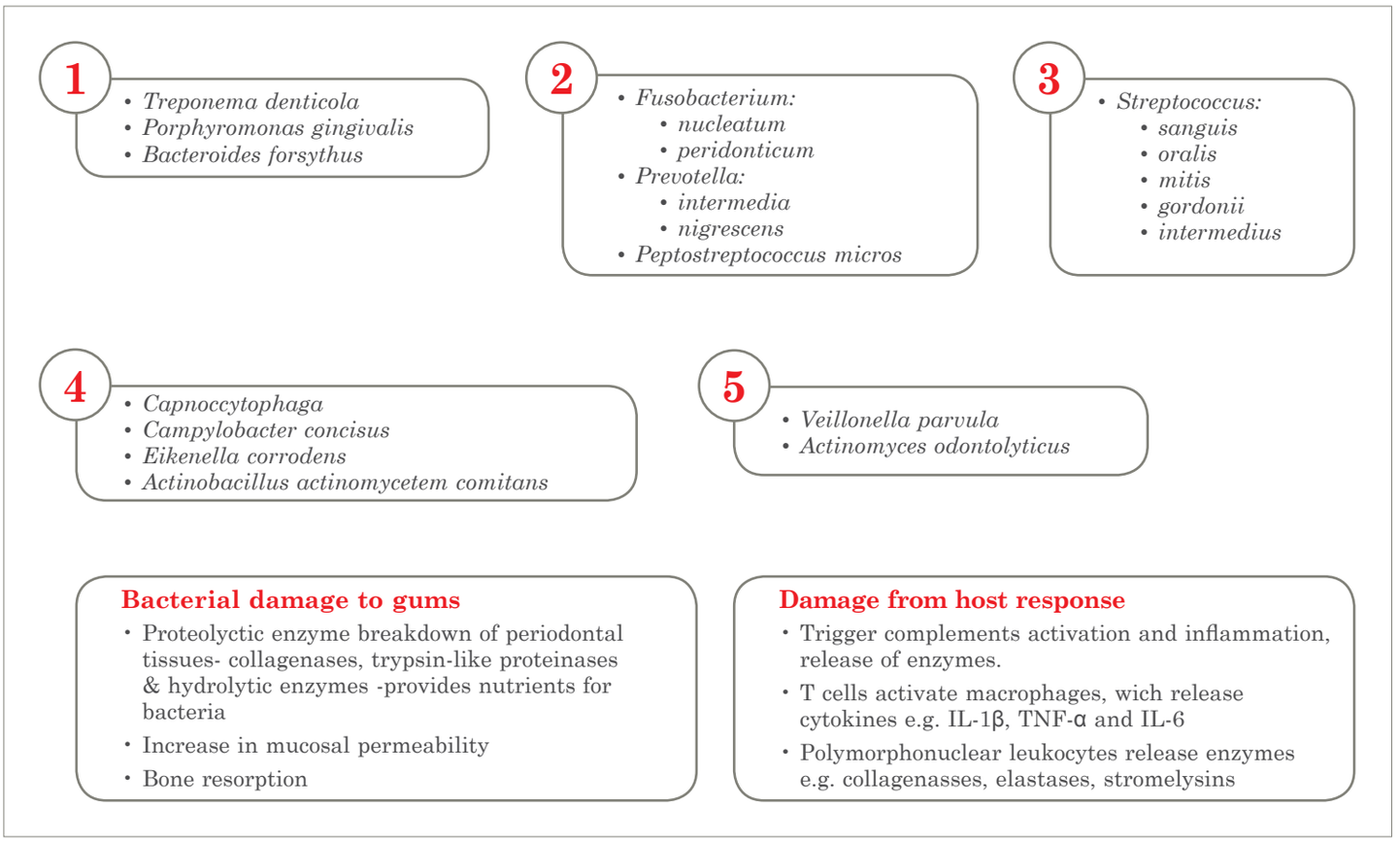

Figure 5.

Some of the oral bacteria implicated in dementia and their affiliations.

Adapted from (Socransky et al. 1998, Hasan & Palmer 2014) Social groupings of bacterial species have been described. It has been suggested that growth factors or other nutrients may be produced by some that are required by others. Group 1 is most strongly associated with clinical measures of periodontal disease especially for pocket depth and bleeding on probing.

Genetic links between AD, inflammation and bone health.
The inflammatory component of AD has long been identified and its relevance noted (Lue et al. 1996, McGeer & McGeer 1999). However, for many reasons, including the fact that anti-inflammatory drugs were not generally successful, the concept was not fully explored. However, more recently new interest has been generated by genome-wide association studies which, when examined in very large cohorts, suggest that genes involved in processes of inflammation are risk factors for AD. Seven genes in particular are of interest here: APOE, TREM2, SHIP1, CD33, CR1, and ABCA7 due to their ability to activate microglia. (Malik et al. 2015). Microglia can be neuroprotective or neurotoxic, or both, depending on other influences.

Intimately associated with bone resorption is the loss of vitamin D, and a number of studies relate lower serum levels of vitamin D with extent of periodontitis. Chronic periodontitis is caused by increased resorption of the alveolar bone, which supports the teeth, and presents with infection and inflammation, so unsurprisingly, genetic polymorphisms in the vitamin D receptor have been associated with periodontitis. Less obvious perhaps is a link between vitamin D and AD. However, Vitamin D elicits neuronal protection by a number of mechanisms including reduction of inflammation, partly by suppressing pro-inflammatory cytokines such as TNF-α, and increased removal of Aβ42 (Kalueff & Tuohimaa 2007, Annweiler et al. 2011); and various studies do show associations of specific vitamin D receptor polymorphisms with an increased risk of onset of AD (Gezen-Ak et al. 2007) particularly in older people over 75 years (Lehmann et al. 2011).

Proposed benefits of periodontal health/treatment for the evaluated disease
The link between periodontal disease and a number of chronic systemic diseases and conditions is now well established. Over the last decade in particular, a large body of research work has demonstrated periodontitis as an independent risk factor for many systemic conditions including atherosclerosis and stroke (Dietrich et al. 2013), coronary heart disease (Schenkein & Loos 2013), adverse pregnancy outcomes (Ide & Papapanou 2013) and diabetes (Borgnakke et al. 2013). Further to these associations, there is now emerging evidence for links between periodontitis with nosocomial pulmonary infections, pancreatic cancer, rheumatoid arthritis and, as shown in this paper, AD.

As indicated earlier in this article, changes in the brain associated with AD have been shown to precede the diagnosis by up to 20 years (Bateman et al. 2012) and suggest that patients should be treated early before the onset of symptoms. The importance of periodontal therapy in periodontal patients may therefore extend beyond the treatment of the immediately apparent oral problem and impart longer-term benefit in reducing their risk of developing AD. For those already suffering with AD, the evidence suggests that periodontal treatment may be able to slow disease progression.

As well as being a risk factor for AD, periodontal disease is also frequently a consequence. Depending on the stage of AD, oral hygiene can be significantly compromised, particularly in the advanced stages. The cognitive processes of learning are affected and attention of the individual is often compromised with the memory being progressively damaged. This means the individual forgets to carry out the brushing process and, when brushing, can't remember how to brush or for how long. Motor skills are also poor (Ghezzi & Ship 2000) and, as the dementia advances, more daily activities are disrupted, often resulting in poor or no toothbrushing. In a susceptible individual this will lead to gingivitis, periodontal disease, bad breath and tooth loss. The final outcomes of periodontal disease are progressively severe destruction of the tooth-supporting apparatus, tooth loss and masticatory dysfunction.

The benefits of treating periodontitis with good self-directed/ carer-led oral hygiene and regular supportive periodontal therapy are multiple and of high impact for AD individuals. Often oral health is not a priority treatment for this sector of society and a recent systematic review found that older people with dementia had worse oral health than older people without dementia (Delwel et al. 2016). Periodontal treatment greatly increases the outcome of maintaining the dentition and stabilizing periodontal disease, improving chewing function, quality of life with social interaction and wellness (Cicciu et al. 2013), with lack of treatment often resulting in oral disability accompanied by poor quality of life, poor nutritional status and compromised speech and aesthetics (Chapple 2014), irrespective of the possible negative effects on AD progression.

SUMMARY

THE SUGGESTED ASSOCIATION between periodontitis and Alzheimer's disease is explained in Figure 6. Oral bacteria associated with periodontitis chronically secrete pro-inflammatory cytokines and LPS (bacterial lipopolysaccharides or endotoxins), which travel into the bloodstream, initiating microglial activation in the brain with subsequent chronic inflammation. Bacteria may also enter the brain via the olfactory tract. Microglial cells in the brain are activated via these mechanisms and by Aβ activation. The overall result is chronic brain inflammation with subsequent neuronal death over decades.

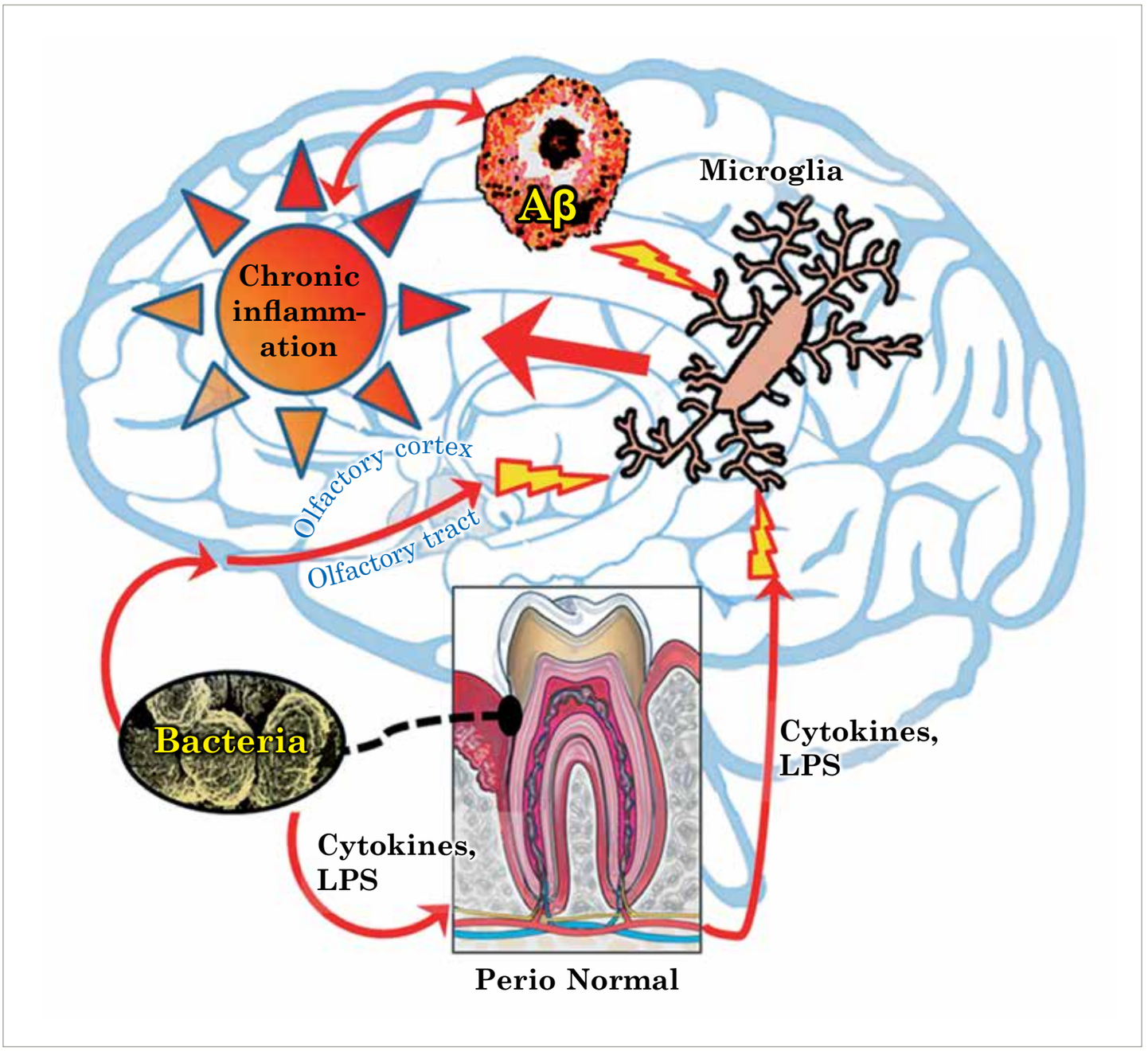

Figure 6.
Suggested association between periodontitis and Alzheimer's disease.
Oral bacteria associated with periodontitis chronically secrete pro-inflammatory cytokines and LPS (bacterial lipopolysaccharides or endotoxins) which travel into the bloodstream, initiating microglial activation in the brain with subsequent chronic inflammation. Bacteria may also enter the brain via the olfactory tract. Microglial cells in the brain are activated via these mechanisms and by Aβ activation. The overall result is chronic brain inflammation with subsequent neuronal death over decades.

CONCLUSIONS

WE HAVE PROVIDED STRONG EVIDENCE to suggest that periodontitis, as a chronic infection, is a likely candidate as an initiator of the cellular, inflammatory phase of AD. By providing stimulus such as LPS and by producing enzymes capable of tissue and bone dissolution, the periodontal bacteria are able to provoke a potentially destructive host response resulting in cytokine infiltration with subsequent microglial activation via peripheral circulation into the brain. They also have close access to the areas of the brain affected in AD, and since there is evidence of their presence in Alzheimer's brain tissue then it is likely that they also penetrate via the olfactory route into the brain. We suggest that treatment for periodontitis should be of primary importance along with an effort to encourage oral hygiene via brushing and attention to the right diet from a young age.

IMPLICATIONS FOR ACTION

FOR THE DENTIST AND FOR THE POPULATION.
For any patient, continuity of care is a valuable attribute for successful dental management. With those living with AD, the benefit of long-term rapport between the dental team and patient/family plays a vital role in the patient-centred approach to treatment. Treatment planning needs to be mindful of the stage of cognitive impairment and working well with the family and carers is crucial to understanding limitations and optimize treatment outcomes. Rigorous oral hygiene measures should be instigated at both home and in the surgery from the outset of diagnosis. In the early stages of dementia, every effort must be made to render the patient dentally fit with restorations of high quality and relatively low maintenance (McNamara et al. 2014). The dental-care plan needs to take into account that, as dementia progresses, the person will be less able to express their needs or wishes, understand and explain oral symptoms such as pain, make decisions and, indeed, give informed consent (McNamara et al. 2014).

The prevalence of severe periodontitis in 2014 was 11%, the global burden of periodontal disease being the sixth most chronic disease of mankind (Kassebaum et al. 2014). These figures are estimated to increase in the future due to increasing life expectancy and a substantial decrease in the prevalence of tooth loss throughout the world from 1990 to 2010 (Kassebaum et al. 2014), although frighteningly, the vast majority of periodontitis cases are totally preventable with good oral care. Figures for comparable years showed there were 46.8 million people worldwide living with dementia in 2015, with numbers estimated to double every 20 years, to 74.7 million in 2030 and 131.5 million in 2050. These new estimates being 12-13% higher than those made for the World Alzheimer Report 2009. Taken individually both AD and periodontal disease have severe consequences for the world population. However, if periodontal diseases could be controlled by excellent oral hygiene and regular supportive dental care, teeth could be maintained with all the advantages described above and AD may possibly be slowed in the early stages with immense benefit for all. Dental and medical healthcare professionals and policy makers need to raise the profile of periodontal disease to ensure the world population is aware of the benefits that can be achieved by improving oral health particularly in our elders, and, further, commit to delivering and supporting this care across all boundaries on a lifelong basis for a better life.

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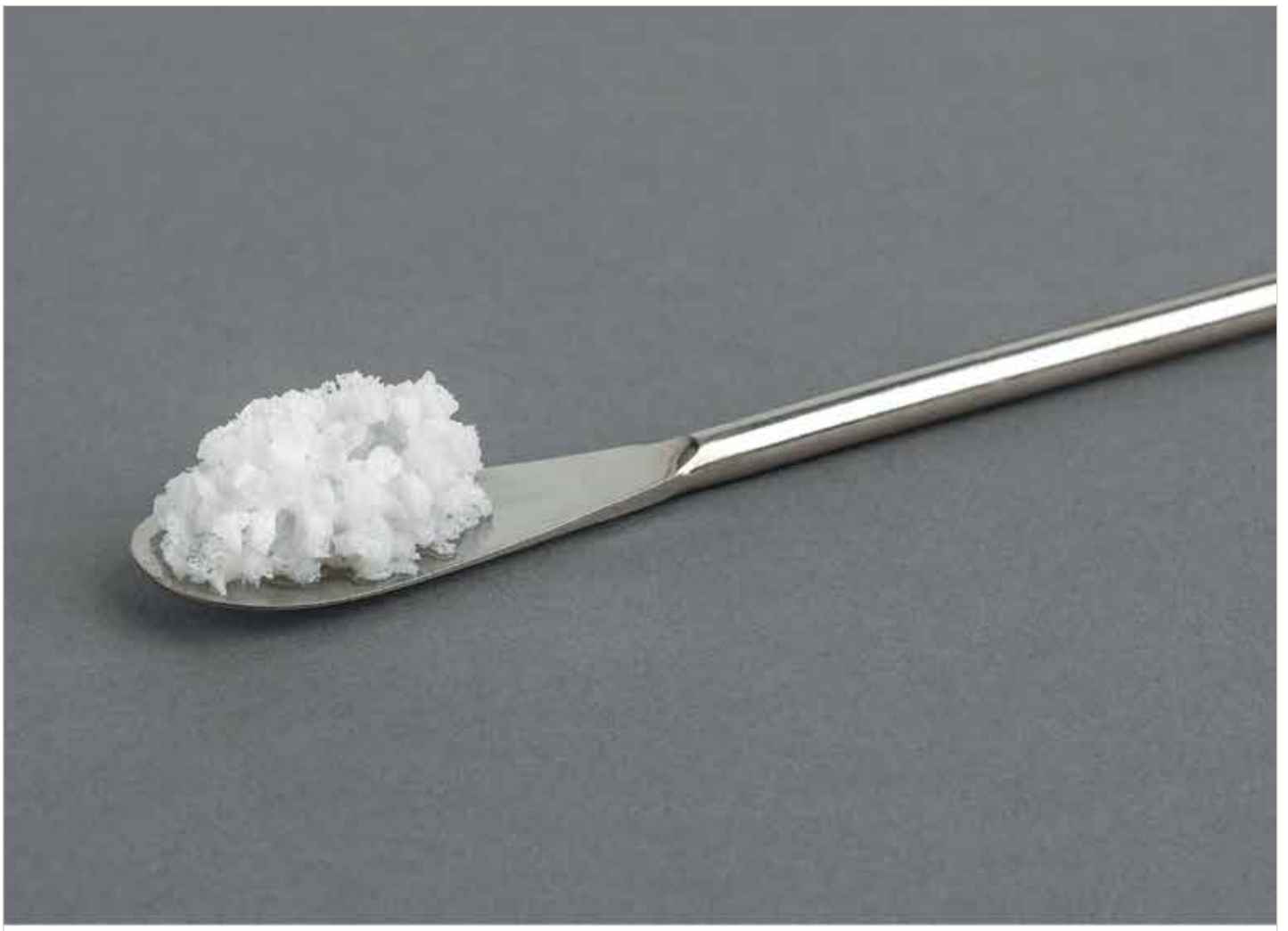

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PERIODONTITIS AND RHEUMATOID ARTHRITIS.

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ABSTRACT

RHEUMATOID ARTHRITIS (RA) is a chronic immune-mediated inflammatory disease that affects between 0.5 to 1% of the world population. RA is characterized by chronic and progressive inflammation of the synovium that leads to destruction of the cartilage and bone. While the cause of RA remains unknown, several epidemiological studies have reported an association between RA and periodontitis. The most accepted hypothesis linking these two diseases is based on *Porphyromonas gingivalis* and its unique capability to citrullinate human and bacterial proteins, which could break the tolerance to citrullinated proteins and start an autoimmune reaction that leads to RA. A few pilot and small studies evaluating the effect of non-surgical periodontal therapy on RA disease activity suggest that treatment of periodontitis may have a significant positive effect on RA but more rigorous clinical controlled trials are needed. If proven, periodontal therapy could be a non-expensive, non-pharmaceutical way of improving RA. In addition, based on the evidence from epidemiological data, patients diagnosed with RA should be advised to visit their dentist and maintain special care with their periodontal health.

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INTRODUCTION

RHEUMATOID ARTHRITIS (RA) is a chronic immune-mediated inflammatory disease that affects between 0.5 to 1% of the world population, in a female/male ratio of 1:3 (Cross et al. 2014, Gabriel & Michaud 2009). The estimated cost of RA for Spain's public health was €590,110,000 in 2005, drugs representing the main component of the direct medical costs, and disability being the main indirect cost (Ruiz-Montesinos et al. 2005).

This common disease is characterized by chronic and progressive inflammation of the synovium that leads to destruction of the cartilage and bone. While the cause of RA remains unknown, the pathobiology characterized by a chronic inflammation of the synovium, infiltrated with inflammatory cells such as macrophages, B cells and CD4+T-cells, and elevated local expression of degradative enzymes, including matrix metalloproteinases (MMP), capable of digesting the extracellular matrix, leading to joint destruction. The rheumatic synovium produces cytokines including tumour necrosis factor (TNF)- α, interleukins (IL) 1, 6, 15, 18 and granulocyte-macrophage colony-stimulating factor (GM-CSF). T-cells and synoviocytes, in the presence of these cytokines, contribute to osteoclast maturation and activation, resulting in bone loss. Ultimately, pannus formation (an anomalous fibrovascular coating) invades and destroys the joint structures (Feldmann et al. 1996, Firestein 2003) leading to deformities and often resulting in functional impairment and disabilities.

In addition, patients with RA have higher risk of developing several co-morbidities such as cardiovascular diseases and their mortality is increased (Aviña-Zubieta et al. 2008).

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) devised a new classification criteria for RA, which includes joint involvement, acute-phase response and antibodies as Rheumatoid Factor (RF) and antibodies against citrullinated proteins (ACPA) (Aletaha et al. 2010). The sensitivity of ACPA for RA ranges between 50-75%, depending on the study, and the specificity is over 95%, being the most disease-specific antibody in RA and may appear before clinical signs and symptoms (Van Venrooij et al. 2002, Niu & Chen 2014).

Treatment of RA aims to reduce inflammation and prevent or retard the destruction of cartilage and bone. Drug therapy is usually a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids (Lipsky et al. 2000).

Biological link between RA and Periodontitis

Similarities between RA and periodontitis have been noted for many years. However, it is still unclear which biological mechanisms explain the interrelation between the two conditions. Different theories have been described based on common pro-inflammatory (IL-1β and TNF-α) and immunoregulatory (IL- 10 and transforming growth factor -TGF-β cytokines), common genetic background (HLA DR-4), and smoking as a common risk factor (Bartold, 2005, Koziel et al. 2014).

A biological hypothesis linking the two diseases is based on *Porphyromonas gingivalis* and its unique capability to citrullinate human and bacterial proteins (Rosenstein et al. 2004). Citrullination is a post-translational modification in which arginine is transformed into citrulline catalysed by the enzyme Peptidyle-Arginine Deiminase (PAD) (Luban & LI 2010) (Figure 1).

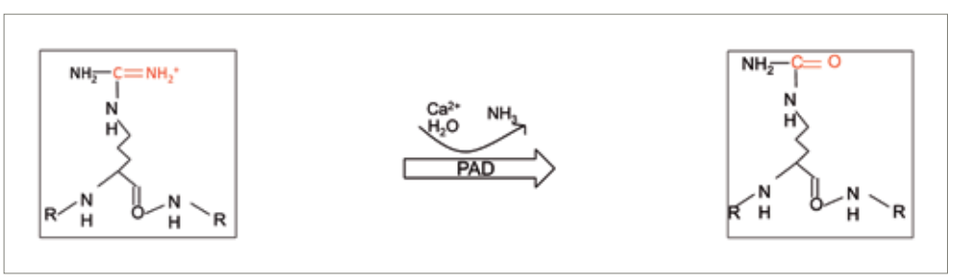

Figure 1.
Protein citrullination by Peptidile-arginine Deiminase (PAD). In the presence of calcium, PAD catalyses the conversion of Arginine to citrulline, changing the ketimine group (=NH) for a ketone group (=O).

Although citrullination occurs as a physiological phenomenon in healthy individuals, the production of auto-antibodies against citrullinated proteins or peptides, is rather specific to RA. Uniquely, *P. gingivalis* has a PAD enzyme – PPAD – which, following the generation of arginine residues by gingipains, is able to citrullinate both internal arginine and terminal arginine both in human and bacterial proteins (Quirke et al. 2014). This creates peptides that would not occur in the absence of *P. gingivalis*, as human PAD can only citrullinate terminal arginine. Through this abnormal citrullination, it has been hypothesized that *P. gingivalis* could break the tolerance to citrullinated proteins and start an autoimmune reaction that leads to RA (Scher et al. 2014, Detert 2010, Koziel et al. 2014, Rosenstein et al. 2004).

A theory has merged the two-hit model described by Golub (Golub et al. 2006) with the role of *P. gingivalis*: the gingival infection by *P. gingivalis* leads to citrullination of bacterial and human proteins. In the presence of signals of inflammation, T-cells and B cells are activated, resulting in antibodies against citrullinated proteins. A second inflammatory event in the joint leads to citrullination of proteins and formation of immune complexes, perpetuating the inflammation and eventually leading to RA (Golub et al. 2006, Lundberg et al. 2010) (Figure 2).

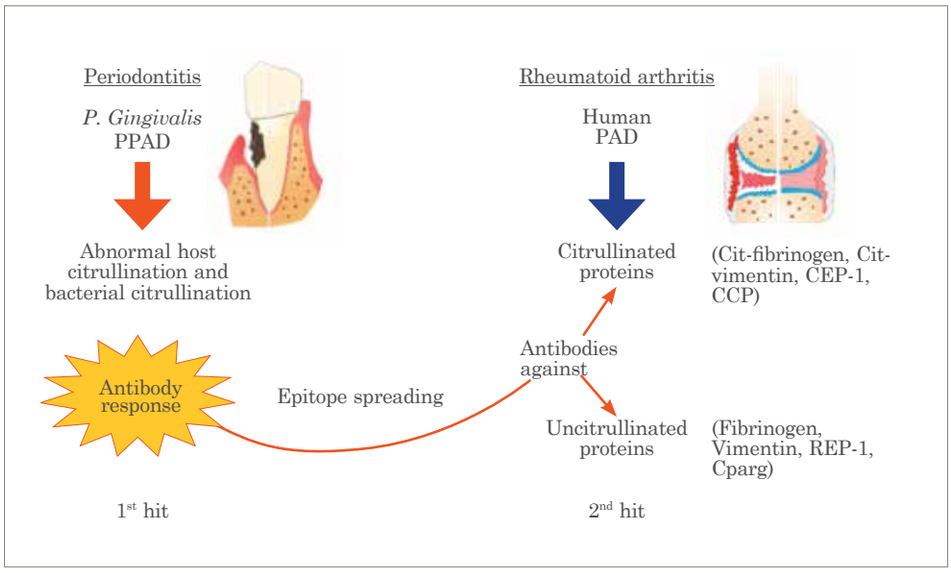

Figure 2.
Two-hit model based on current literature (Golub et al. 2006, Lundberg et al. 2010).

More recently, other periodontal pathogens have been identified as possible triggers for RA. Among the different periodontal pathogens and oral commensals investigated in a recent study, only *Aggregatibacter actinomycetemcomitans* could induce hypercitrullination of human neutrophils. *A. actinomycetemcomitans* induces neutrophil hypercitrullination through the secretion of leukotoxin A (LtxA), a bacterial pore-forming toxin that induces calcium influx and subsequent hyperactivation of PAD enzymes in the neutrophil. Interestingly, the effect of human lymphocyte antigen-DRB1 shared epitope alleles on auto-antibody positivity was limited to RA patients who were exposed to *A. actinomycetemcomitans*. These studies identify the periodontal pathogen *A. actinomycetemcomitans* as a candidate bacterial trigger of autoimmunity in RA.

Although promising, none of the theories described explains why this inflammatory response, hypothetically initiated or exacerbated by periodontitis, would be specific to the joint structure in RA. Further research is needed to clarify the gaps in the literature in this matter since, if proven, periodontitis prevention and therapy could ameliorate the progression of RA.

Table 1. Summary of observational studies published since 2000 (study population>60) studying the association between rheumatoid arthritis (RA) and periodontitis.

Author & Year	Study population	Results	Type of study
(Mercado et al. 2000)	1,412 patients attending dental hospital	Periodontitis: higher prevalence of RA (3.95%)	Cross-sectional
(Mercado et al. 2001)	65 patients (RA vs. non-RA)	RA: higher number of missing teeth, deeper pockets. No difference in bleeding or plaque index	Case control
(Marotte et al. 2006)	147 patients (RA)	Association between periodontal bone loss and wrist bone destruction (χ^2=11.82) and shared epitope HLA-DR	Cross-sectional
(de Pablo et al. 2008)	4,461 patients (NHANES III)	RA: higher prevalence of periodontitis (OR:1.82), edentulous (OR:2.27), less decay (p<0.001)	Cross-sectional
(Pischon et al. 2008)	109 patients (57 RA, 52 non-RA)	RA: higher prevalence of periodontitis (OR:8.05), statistically significant after adjusting to confounding factors (PlI, GI)	Case control
(Dissick et al. 2009)	69 RA patients vs. 35 osteoarthritis (controls) patients	-RA: higher prevalence of periodontitis and more severe -RA patients with periodontitis associated with RF positive and anti-CCP	Case control
(Arkema et al. 2010)	81,132 patients (Nurses' Health Study prospective cohort)	No evidence of higher incidence of RA in periodontitis	Cohort
(Demmer et al. 2011)	9,702 patients (NHANNES I)	Periodontitis: higher prevalence of RA (OR:2.05)	Cross-sectional
(Potikuri et al. 2012)	91 RA (DMARD naive, non-smokers) vs healthy controls	RA: higher prevalence of periodontitis (OR:4.28)	Case control
(Smit et al. 2012)	95 RA, 420 matched controls	RA: higher risk of periodontitis (RR: 3.7)	Cross-sectional
(Chen et al. 2013)	13,779 newly diagnosed RA, 137,790 non-RA	periodontitis: higher prevalence of RA (OR:1.16) ,	Cohort study
(Monsarrat et al. 2014)	74 RA patients	94% of RA had periodontitis (48% moderate and 46% severe)	Cross-sectional
(Eriksson et al. 2016)	2,740 RA cases and 3,942 non-RA	No difference in periodontitis prevalence between groups	Case control

OR, odds ratio; **RR,** risk ratio; **PlI,** plaque index; **GI,** gingival index; **RF,** rheumatoid factor; **anti-CCP,** anti-cyclic Citrullinated Peptide.

Epidemiological evidence

Several epidemiological studies have reported an association between RA and periodontitis (Table 1).

In cross sectional studies, researchers found that, compared to patient without RA, patients with RA showed a significantly increased prevalence of periodontitis, with odds ratio (OR) ranging between 1.82 (de Pablo et al. 2008) and 8.1 (Pischon et al. 2008). Furthermore, patients with periodontitis have higher prevalence of RA, with odds ranging between 1.16 (Potikuri et al. 2012) to 2.05 (Demmert et al. 2011). Studies show that this relationship is independent of smoking (Potikuri et al. 2012), oral hygiene (plaque) (Mercado et al. 2001, Pischon et al. 2008) and genetic factors (Marotte et al. 2006).

In the NHANES data reported by De Pablo et al., 50% of subjects the RA patients were identified as edentulous, with these patients maybe representing severe cases of periodontitis (de Pablo et al. 2008). In the OSARA study, researchers found that from 74 RA patients examined, 94% suffered from moderate to severe periodontitis (48% moderate and 46% severe) (Monsarrat et al. 2014)

Case-control studies also show a higher prevalence of periodontitis in RA patients compared to controls, with OR ranging between 4.28 (Potikuri et al. 2012) to 8.03 (Pischon et al. 2008), after adjusting for confounding factors such as plaque and gingival indices.

Table 2. Clinical trials evaluating the effect of periodontal therapy in rheumatoid arthritis (RA).

Author	Year	Follow-up	Patient number	Parameters evaluated	Results
(Ribeiro et al. 2005)	2005	3 months	42 RA+PD -16 periodontal treatment -26 oral hygiene and supragingival cleaning	RF, ESR, HAQ	RF significantly reduced
(Al-Katma et al. 2007)	2007	8 weeks	29 RA+PD -17 periodontal treatment -12 no treatment	DAS 28, ESR	VAS, DAS and ESR reduced
(Ortiz et al. 2009)	2009	8 weeks	40 RA+PD -10 periodontal treatment and DMARDs only. -10 periodontal treatments and DMARDs with anti-TNF drugs. -10 no periodontal therapy, DMARDs only -10 no periodontal treatment, DMARDs with anti-TNF drugs.	ESR, TNF-alpha, signs and symptoms	VAS and DAS improved in treatment groups. ESR not significantly reduced Anti-TNF drugs improved PPD and CAL
(Pinho et al. 2009)	2009	6 months	75 patients: -15 RA+PD with periodontal treatment -15 RA+PD no periodontal treatment -15 PD with periodontal treatment -15 PD no periodontal treatment	DAS 28, CRP, ESR, AAG (alpha-1 acid glycoprotein)	No clear relation. AAG, ESR and CRP not significantly reduced with periodontal therapy.
(Okada et al. 2013)	2013	8 weeks	55 RA+PD -26 supragingival cleaning -29 no treatment	DAS 28, CRP, anti-CCP, RF, TNF-alpha and levels of IgG to P. gingivalis	Reduction of DAS 28 and levels of IgG to P.gingivalis and citrulline.
(Erciyas et al. 2013)	2013	3 months	60 RA and PD -30 RA moderate-severe disease activity -30 RA low disease activity	ESR, CRP, TNF-alpha, DAS28	Significant reduction of ESR, CRP, TNF-alpha, DAS28

PD, periodontitis; **RA,** Rheumatoid Arthritis; **RF,** Rheumatoid Factor; **ESR,** Erythrocyte Sedimentation Rate; **HAQ,** Health Assessment Questionnaire; **DAS,** Disease Activity Score; **VAS,** Visual Analogue Scale; **TNF,** Tumor Necrosis Factor; **CRP,** C-Reactive Proteins; **AAG,** alpha-1 acid glycoprotein.

However, there are also studies that did not find such associations. In a large cohort study, using data from 91,132 nurses followed over 12 years, there was no evidence of a higher risk of developing RA patients among those with periodontitis; however, periodontitis was defined based on history of periodontal surgery and therefore included individuals with treated and not active periodontitis (Arkema et al. 2010). More recently, no difference in the prevalence of periodontitis was observed in a Swedish case-control study including 2,740 RA patients in whom periodontitis was defined by self-reporting (Eriksson et al. 2016).

It has been discussed whether the association between RA and periodontitis is due to the functional disability of RA patients that might limit their oral hygiene. However, studies have failed to show a difference in plaque control between patients with RA compared to healthy controls (Torkzaban et al. 2012, Mercado et al. 2001, Pischon et al. 2008). Other confounding common risk factors like tobacco and the presence of alleles HLA-DBR1 have also been considered, but are unlikely to explain the association (Marotte et al. 2006, Potikuri et al. 2012).

A systematic review, considering all the findings from observational and experimental studies, found evidence for an association between RA and periodontitis, but identified a need of larger and rigorous studies in well-characterized populations to evaluate the association (Kaur et al. 2013, De Pablo et al. 2009).

Proposed benefits of periodontal treatment in RA

A few pilot and small studies, evaluating the effect of non-surgical periodontal therapy on RA status, suggest that treatment of periodontitis may have a significant positive effect on RA severity (Table 2).

Due to the high prevalence of periodontitis, it may represent an important modifiable factor for RA incidence and severity. If proven, treatment of periodontitis could be an inexpensive and safe non-pharmacological treatment with direct benefit for patients with RA.

However, there are shortcomings in the current literature: these clinical studies have a short follow-up period (ranging between 8 weeks and 6 months) and have a small sample size. Furthermore, each study uses different definitions of periodontitis and uses different parameters to measure RA status, the most commonly used being the Disease Activity Score (DAS28), based on subjective measures such as the Visual Analog Scale (VAS) and number of tender joints. Due to the heterogeneity in all the studies connecting RA and periodontitis, a systematic review with meta-analysis (Kaur et al. 2014) could include only a few of the multitude of parameters studied. Erythrocyte sedimentation rate (ESR) was the only parameter that significantly decreased after periodontal treatment (Ortiz et al. 2009).

In the joint Workshop of the European Federation of Periodontology and the American Academy of Periodontology, in 2013, group 4 concluded that more rigorous clinical controlled trials and research were needed in the field (Linden & Herzberg 2013).

SUMMARY AND CONCLUSIONS

ALTHOUGH THERE IS EVIDENCE of the epidemiological link between RA and periodontitis, the direction of this relationship is not known. Longitudinal and case-control studies are needed to explore if periodontitis increases the risk of RA manifestation. While a few small clinical studies show a trend in an amelioration of RA surrogate parameters after periodontal treatment, more controlled clinical trials with longer follow-up periods and larger number of patients are needed to corroborate this hypothesis. If proven, periodontal therapy could be a non-expensive, non-pharmaceutical way of improving RA in addition to of the known local and systemic benefits of maintaining periodontal health.

IMPLICATIONS FOR ACTION

BASED ON THE EVIDENCE from epidemiological data, patients diagnosed with RA should be advised to visit their dentist and maintain special care with their periodontal health, as they have a higher risk of suffering from chronic periodontitis than the rest of the adult population.

Dentists treating patients with known chronic periodontitis should be aware of the higher risk they have of developing RA and it would be beneficial if they recognized early signs and symptoms such as morning stiffness, swelling and pain of joints and movement limitation.

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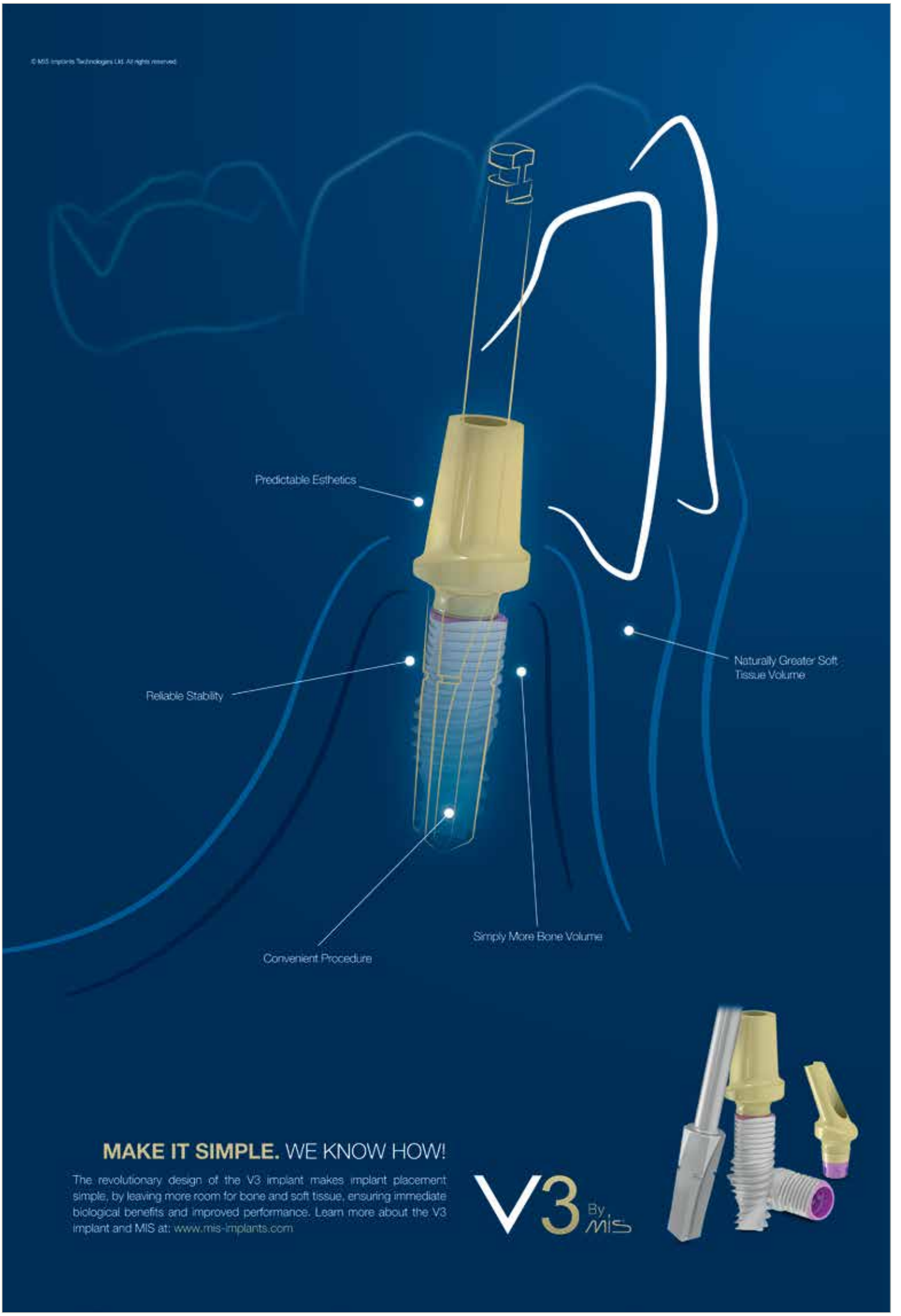

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quality of life

quality of life

THE SYSTEMIC BENEFITS OF PERIODONTAL HEALTH: QUALITY OF LIFE.

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ABSTRACT

THE AIM OF THIS ARTICLE is to critically appraise the evidence underpinning the perception of the quality of life and periodontal status. Periodontal status strongly influences quality of life. Subjects with periodontal diseases show a lower level of Oral Health Related Quality of Life (OHRQoL) with many individuals experiencing significant effects on comfort, breath odour, function, physical psychological and social aspects. Nevertheless, periodontal treatment is capable of improving OHRQoL and overall psychological status. Clinicians may be proficient in understanding OHRQoL measures as they are directly related to the patient's well-being.

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HEALTH AND QUALITY OF LIFE

HEALTH IS A COMPLEX BALANCE that cannot be defined simply by the absence of a certain disease. Accordingly, health is a "a complete state of physical, mental, and social well-being" (World Health Organization 2006). It is, thus, easily comprehensible that a status of health may not be achieved unless all the clinical and non-clinical scenarios surrounding a peculiar disease are under control. Therefore, a clear and educated knowledge of the possible impact of a disease and its treatment on outcomes that are related to social well-being and psychology is mandatory for a modern approach to clinical practice. Accordingly, measures of quality of life have been considered a reliable tool to assess well-being.

The World Health Organization has defined the quality of life (QoL) as "perceptions of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns" ('The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization.' 1995). Quality of life is the result of an interaction between and among health conditions, social and contextual factors and it is thus highly subjective and changeable throughout time; it influences "the degree to which a person enjoys the important possibilities of life as well-being is maintained" (Locker et al. 2005). The WHOQOL is organized into six broad domains of quality of life. These are: (a) physical domain, (b) psychological domain, (c) level of independence, (d) social relationships, (e) environment and (f) spirituality/religion/personal beliefs ('The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization.' 1995). Thus, self-consciousness, nearness and intimacy are overall aspects that may be strongly influenced by alteration of the WHOQOL (Figure 1).

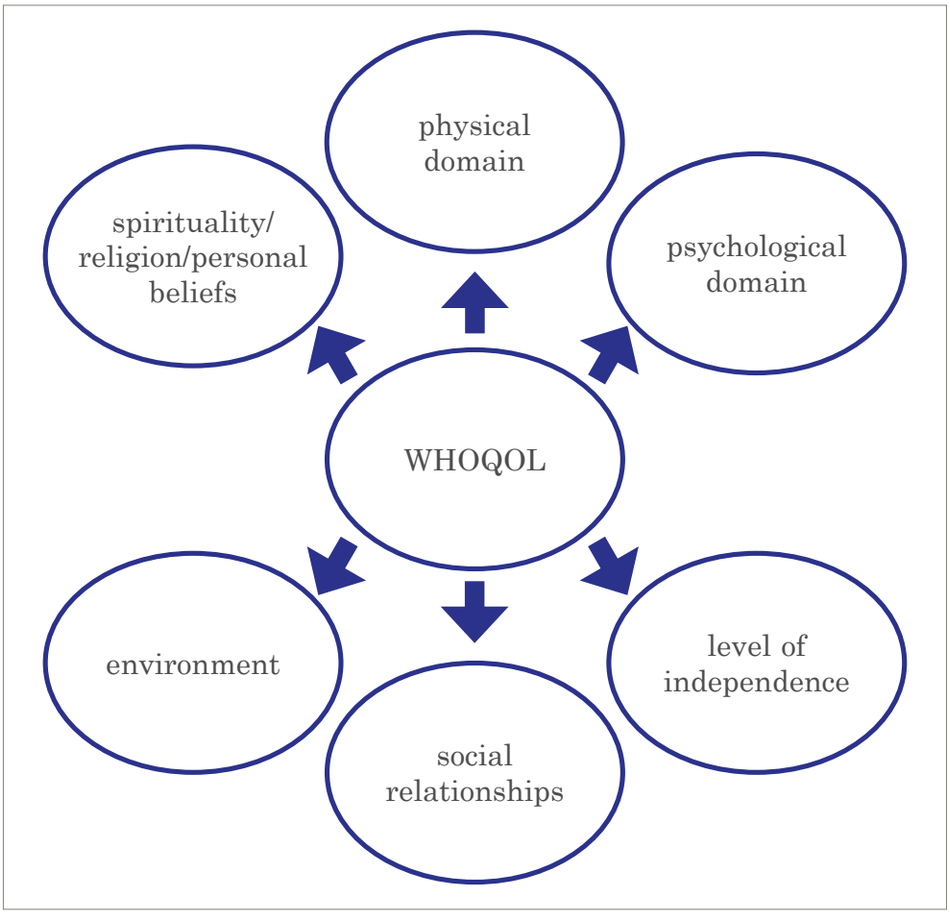

Figure 1.
The World Health Organization Quality of Life assessment (WHOQOL) domains ('The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization.' 1995).

Quality of Life has been increasingly studied in Dentistry as oral health may significantly affect the individual's perception of quality of life. An entire research field has been developed to measure oral health-related quality of life (OHRQoL) (Locker & Allen 2007). The presence of OHRQoL in dental literature assessing the impact of specific oral conditions has increased significantly over the last twenty years.

Traditionally, clinicians monitor the periodontal status through outcomes such as clinical attachment level, probing pocket depth, plaque and bleeding on probing. These outcomes are of uttermost importance for professionals. However, they provide no information about the patient's perspective and perception of the disease and its impact on overall health (Allen 2003, Jönsson & Öhrn 2014). Indeed, these outcomes have been defined as surrogate outcomes as opposed to the "true" outcomes (Hujoel 2004). Surrogate outcomes are intangible to the patient's appreciation and capacity of discern although, as they can be measured by a clinician, conserve an objective nature. "True" outcomes (i.e. tooth loss, gingival bleeding after brushing, aesthetic satisfaction after muco-gingival surgery, etc.) can be easily identified by both the patient and the clinician. True outcomes are also defined as Patient-Based Outcomes (PBOs) (Shanbhag et al. 2012, Tsakos et al. 2010). PBOs are used as to complement surrogate measures supporting the clinician in understanding the effects of disease/treatment on symptoms, functioning and psychosocial factors such as OHRQoL and treatment satisfaction (Wyrwich et al. 2013).

OHRQoL measures consists of questionnaires evaluating only meaningful true outcomes allowing the evaluation of the impact of the status of health of the oral cavity on the patient's daily life (Sischo & Broder 2011). It allows to investigate different factors such as function (chewing, speaking), psychological aspects (appearance, self-esteem), social perception (intimacy, attractiveness, anxiety), oral health (pain/discomfort, gum bleeding), treatment expectations (satisfaction) and environment (school, job) (Sischo & Broder 2011, Bennadi & Reddy 2013). In order to investigate OHRQoL, different questionnaires/interviews have been proposed varying among them in terms of number of questions or areas investigated (Bennadi & Reddy 2013). Each question may be answered by the patient with multiple options usually indicating the frequency in time of a feeling/sensation related to the quality of life affected by the oral health status. Questions such as "have you ever felt tense because your mouth" constitutes an example a question of a questionnaire investigating OHRQoL.

HOW COULD ORAL HEALTH AFFECT QUALITY OF LIFE?

THE MECHANISMS UNDERLYING the connection among oral health and quality of life are complex, multi-faceted and strongly influenced by subjectivity. Indeed, quality of life may be altered by the overall oral condition irrespectively of the single contribution of one specific disease, and it is somewhat ethereal and heavily imbued with elusiveness and subjectiveness of values.

Nevertheless, it is possible to trace some of the key aspects that may lead to lowering the quality of life of a periodontally affected subject. Indeed, some specific areas are involved: symptomatology, functionality and psychology. Oral diseases could affect quality of life directly through pain but "also more subtly from effects such as increased systemic inflammation and psychosocial impacts" such as impaired confidence and socialization (Needleman et al. 2015).

Periodontal diseases symptoms swollen gums, sore and receding gums, drifting teeth bad breath deeply affect the physical, social and psychological aspects of patients' quality of life (Beikler & Flemmig 2011). Individuals affected by periodontitis feel that the disease may have an impact on their function, comfort, appearance and self-confidence (Needleman et al. 2004). Indeed, OHRQoL is strictly related to symptoms such as sore or receding gums, tooth mobility and oral malodour.

Function is also essential in the maintenance of well-being. Indeed chewing function may indeed be related to the residual dentition (Osterberg & Steen 1982). Tooth loss being the most important sign of periodontitis, it is evident that there might be a connection. The loss of posterior teeth decreases the ability to eat all meals, predisposing the patient to an incorrect diet and can lead to an incorrect occlusion with the consequence of pain, loss of function and temporomandibular disorders (Sheiham et al. 2001). Chewing function disruption reduces nutritional intake and it is related to neurological diseases (Koller 1983, Blanchet et al. 2008, Kosaka et al. 2014). Indeed, tooth loss is related to impaired OHRQoL (Gerritsen et al. 2010).

Moreover, tooth loss has a direct effect on the aesthetical appearance and social well-being, being associated with limitation in laughing in public, forming relationships and enjoying food, leading to an overall loss of self-confidence (Craddock 2010). Additionally, anterior tooth loss affects the patient's quality of life not only for an aesthetic problem, but also because it influences the ability to pronounce words correctly.

The close relationships among periodontal diseases and psychosocial status may also partly explain the impact on OHRQoL. Work load, social class, lack of sleep and lifestyle (Marcenes & Sheiham 1992, Abegg et al. 1999) predispose individuals to periodontal diseases and oral-health high-risk behaviours (Croucher et al. 1997). Daily hassles, major life events and systemic illness are all important factors that can lead to an allostatic load unbalance, altering the ability to adapt successfully to a changing environment. Stress is therefore associated with periodontitis through both direct and indirect mechanisms (Boyapati & Wang 2007). On the one hand, an accumulation of allostatic load is related to unhealthy behaviors, such as smoking, alcohol abuse, sleep deprivation and poor oral hygiene, thus increasing the susceptibility to periodontitis (Borrell & Crawford 2011). High working load with low flexibility (inability to make private phone calls, receive visitors and leave for private reasons during worktime) causes a reduction of the quality of life and decreases the care of the person. Individuals with a stricter working schedule are more likely to clean their teeth less often, consequently having higher levels of dental plaque (Abegg et al. 1999). On the other hand, stress also affects the autonomous nervous system and the immune system via activation of the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal medullary axes which results in increase of cathecolamin and cortisol levels (Padgett & Glaser 2003). Salivary cortisol levels are higher in patients with severe periodontitis, high financial stress and inadequate coping, as compared to a control group (11.04 ± 4.4 vs. 8.6 ± 4.1 nmol/L salivary cortisol, respectively) (Genco et al. 1998). Thus, subjects experiencing an alteration of their allostatic balance may easily show an enhancement of the inflammatory propensity.

Self-confidence and appreciation of social life, people and experiences is one of the most essential characteristics of human beings and it is densely connected to the perception of happiness and quality of life. Strikingly, periodontitis-affected subjects tend to show lower level of life's enjoyment. When periodontal patients were taped and measured while watching funny TV shows, the capability of smiling with wide-mouth aperture and the frequency of smiling was affected (Patel et al. 2008). Patients considered periodontitis as a shameful disease and as something they would rather not talk about (Abrahamsson et al. 2008). The feelings frequently expressed were fear (i.e. of tooth loss), shame (avoidance of food, people, hands covering the mouth while smiling) and anger (against the previous dentist that had not alerted them before about periodontitis).

Table 1. OHIP-14 individual items response (Slade 1997).

Dimension	Oral Health Impact Profile-14
Functional	Have you had trouble *pronouncing any words* problems with limitations to your teeth, mouth or dentures? Have you felt that your *sense of taste* has worsened because of problems with your teeth, mouth or dentures?
Physical pain	Have you had *painful aching* in your mouth? Have you found it *uncomfortable to eat any foods* because of problems with your teeth, mouth or dentures?
Psychological discomfort	Have you been *self-conscious* because of your teeth, mouth or dentures? Have you *felt tense* because of problems with your teeth, mouth or dentures?
Physical disability	Has your *diet been unsatisfactory* because of problems with your teeth, mouth or dentures? Have you had to *interrupt meals* because of problems with your teeth, mouth or dentures?
Psychological disability	Have you found it *difficult to relax* because of problems with your teeth, mouth or dentures? Have you been a bit *embarrassed* because of problems with your teeth, mouth or dentures?
Social disability	Have you been a bit *irritable* with other people because of problems with your teeth, mouth or dentures? Have you had *difficulty* doing your usual jobs because of problems with your teeth, mouth or dentures?
Handicap	Have you felt that life in general was *less satisfying* because of problems with your teeth, mouth or dentures? Have you been *unable to function* because of problems with your teeth, mouth or dentures?

Responses are made on a 5-point scale, coded **0** = never, **1** = hardly never, **2** = occasionally, **3** = fairly often, **4** = very often.

HOW TO MEASURE ORAL-HEALTH-RELATED QUALITY OF LIFE?

OHRQOL IS ASSESSED THROUGH THE USE OF DIFFERENT questionnaires or interviews as being deeply rooted in the patient's experiential appreciation of life. There are indeed various measures for assessing different aspects of OHRQoL (Locker & Allen 2007). The most commonly used questionnaires are the Oral Health Impact Profile OHIP-14, 20, 49 (Slade & Spencer 1994), the General Oral Health Assessment Index GOHAI (Atchison & Dolan 1990), the Oral Impacts on Daily Performance OIDP (Adulyanon, Supreda & Sheiham 1997) and the UK oral-health-related quality-of-life measure (OHQoL-UK®) (McGrath & Bedi 2001, Mcgrath & Bedi 2002).

The Oral Health Impact Profile (OHIP, Table 1) has been described as 49 unique statements grouped in 7 conceptual subscales. The seven groups were: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap (Slade 1997). The necessity of a more succinct instrument to assess the perceived impact of oral health as one of several outcomes of dental care promoted the development of OHIP-14 (Slade 1997). However, this text did not include statements relevant to denture wearing and, for this reason, an enlarged version, the OHIP-20, was developed to be used in clinical trials of prosthodontic procedures (Allen & Locker 2002). OHIP-14 has been widely used in Periodontology (Ng & Leung 2006, Jönsson & Öhrn 2014).

Table 2. GOHAI, General Oral Health Assessment Index (İlhan et al. 2015, Atchison & Dolan 1990).

Item	GOHAI, General Oral Health Assessment Index
Physical function	How often did you limit the kinds or amounts of food you eat because of problems with your teeth or dentures? How often did you have trouble biting or chewing any kinds of food such as firm meat or apples? How often were you able to swallow comfortably? How often have your teeth or dentures prevented you from speaking the way you wanted?
Pain/Discomfort	How often were you able to eat anything without feeling discomfort? How often did you limit contacts with people because of the condition of your teeth and gums, or dentures? How often were you pleased or happy with the looks of your teeth and gums, or dentures? How often did you use medication to relieve pain or discomfort from around your mouth?
Psychosocial	How often were you worried or concerned about problems with your teeth, gums, or dentures? How often did you feel nervous or self-conscious because of problems with your teeth, gums, or dentures? How often did you feel uncomfortable eating in front of people because of problems with your teeth or dentures? How often were your teeth or gums sensitive to hot, cold, or sweets?

Responses are made on a 6-point scale, coded **0** = never, **1** = seldom, **2** = sometimes, **3** = often, **4** = very often, **5** = always.

Table 3. OIDP, Oral Impacts on Daily Performance (Adulyanon, Supreda & Sheiham 1997, Astrøm & Okullo 2003).

Oral Impacts on Daily Performance
"During the past 6 months how often have problems with your oral and dental health caused any difficulty with":
1. Eating
2. Speaking
3. Cleaning teeth
4. Sleeping/relaxing
5. Showing teeth
6. Emotional status
7. Carrying out work
8. Enjoying social contact

Responses about frequency of dental problems were scored on a 5-point scale. In periodontology, the frequency of the impact is important: **0** = never affected, **1** = less than once a month, **2** = once or twice a month, **3** = once or twice a week, **4** = every or nearly every day.
The same responses are also used to assess severity, normally scored on a 6-point scale: **0** = none, **1** = very little, **2** = little, **3** = moderate, **4** = severe, and **5** = very severe.

The GOHAI (Table 2) is a self-reported compact questionnaire of 12 items that evaluates problems related to oral health and the severity of the associated psychosocial impacts in the past 3 months. The measure includes items regarding freedom from pain and infection, and the respondent's ability to continue in his or her desired social roles (Sánchez-García et al. 2010). The impact of oral disorders on health-related quality of life is calculated by assigning an overall score to indicate the extent of a range of functional and psycho-social consequences.

The Oral Impacts on Daily Performance (OIDP, Table 3) index refers to the ability to carry out 8 daily tasks: eating and enjoying food, speaking and pronouncing clearly, cleaning teeth, sleeping and relaxing, smiling, laughing and showing teeth without embarrassment, maintaining usual emotional state without being irritable, carrying out major work or social role and enjoying contact with other people (Allen 2003). OIDP partly addresses one of the potential problems arising from the usage of the questionnaires: the alteration of OHRQoL may not be specifically related to one single disease but to a multiplicity of oral conditions (Tsakos et al. 2010).

The UK oral-health-related quality of life measure (OHQoL-UK®, Table 4) has been developed for investigate the impact of oral diseases on the quality of life, specifically for the UK population (McGrath & Bedi 2001, Mcgrath & Bedi 2002). Indeed, the quality of life and individual perceptions and needs are influenced by experiences, uses, living environment and the economy of different countries (Scheppers et al. 2006).

Table 4. Unweighted version of OHQoL-UK (Mcgrath & Bedi 2002).

UK oral-health-related quality of life measure	
Domain	**"What effect does your teeth, gums, mouth and/or false teeth have on each of the 16 key areas" ?**
Physical	Eating/enjoyment of food Appearance Speech General health Comfort Breath odour
Social	Social life Romantic relationships Smiling or laughing Work/ability to do usual jobs Finances
Psychological	Confidence Sleep/ability to relax Carefree manner Mood Personality

Responses were scored on a 5-point scale: **1** = very bad, ***2*** = bad, **3** = none, **4** = good, **5** = very good.

PROPOSED BENEFITS OF PERIODONTAL HEALTH/ TREATMENT FOR OHRQOL

1. OHRQoL and periodontal health status

Periodontal health status shows an impact on OHRQoL when comparing disease subjects versus not-affected ones. Ng & Leung compared the average OHIP-14 scores of 767 subjects belonging to two different groups: "healthy/low periodontal attachment level subject group" (full-mouth mean clinical attachment level CAL <2 mm) to a 'high/severe periodontal attachment loss group" (full-mouth mean CAL >3 mm) (Ng & Leung 2006). They found significant differences for functional limitations, physical pain, psychological discomfort, and physical and psychological disabilities in the two groups. Moreover, high/severe CAL status was significantly associated with job strain, financial strain, depression and trait anxiety. In a periodontal population with radiographical loss of supporting bone tissue of at least 1/3 of the root length in at least 30% of the dentition, a reduced quality of life, in the OHIP-14 score, was noted when compared with other periodontal subjects (Jansson et al. 2014).

The extension and the severity of the disease may in fact affect the perception of quality of life: the higher the periodontal involvement, the more OHRQoL is affected. In 2004, Needleman published the results of 205 patients attending a private periodontal clinic assessed with OHQoL-UK® (Needleman et al. 2004). The effect of periodontal status on quality of life was considerable, with many individuals experiencing significant effects in terms of symptoms (comfort, 19%; breath odour, 18%), physical aspects (eating, 14%; appearance, 18%), psychological aspects (influence on mood, 12%; carefree manners 15%), and social aspects (finances, 32%; happiness 12%). Interestingly, the OHRQoL scores of the subjects correlated significantly with the number of teeth with probing depths >5 mm, underpinning the concept that there might be a connection between periodontal destruction and overall quality of life. The already quoted effect on smiling wideness was also, in fact, related to the severity (number of pockets) of the disease (Patel et al. 2008). Thus, the overall evidence is that there is a dose-response relationship between periodontal disease and OHRQoL with greater impact with increasing severity or extent of the disease (Buset et al. 2016).

Finally, one should bear in mind the potential aesthetic-related alterations of quality of life. Individuals with gingival recession of at least 2 mm had an approximately two times higher chance of having a negative impact than individuals without recession, when recession was located in the anterior teeth (Wagner et al. 2016). Increasing extent of recession was associated with lowering of OHRQoL.

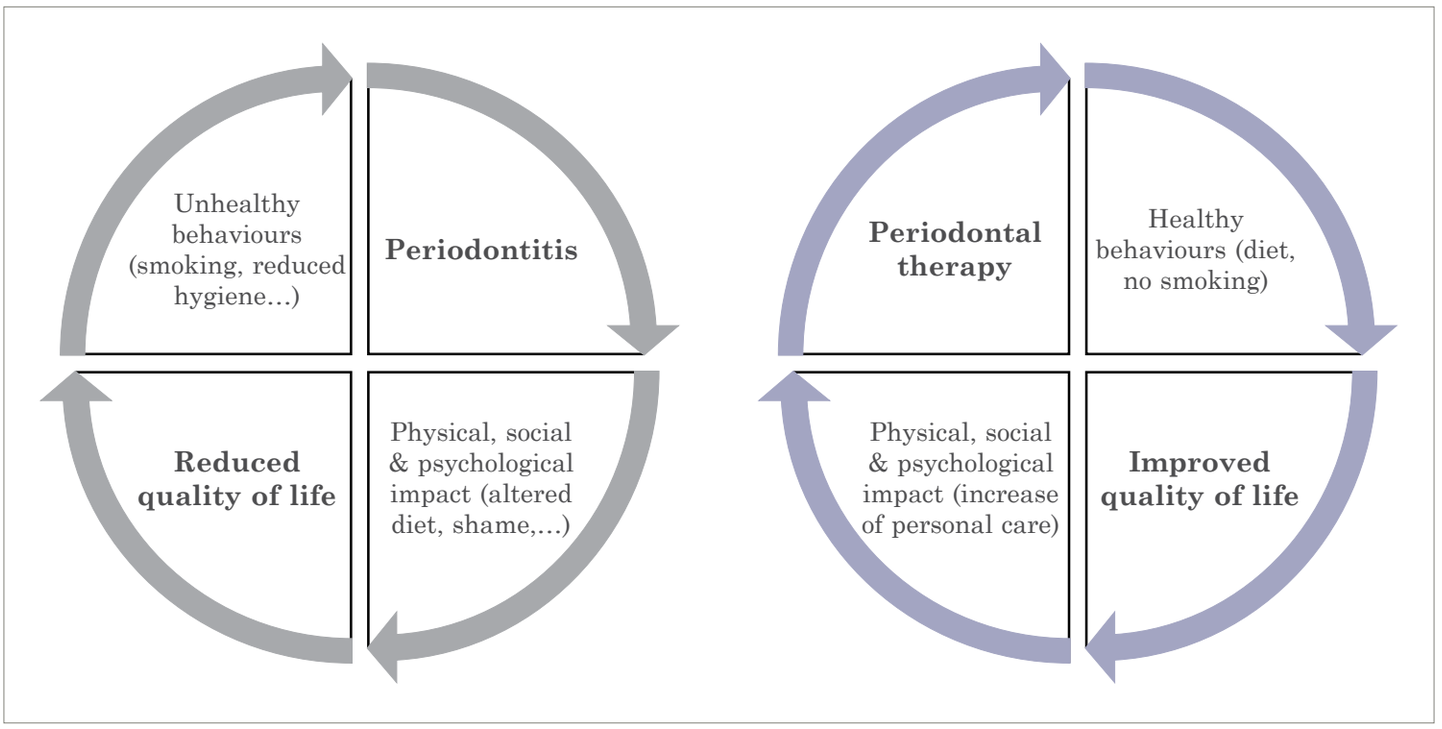

Figure 2.
The relationship between periodontitis and poor quality of Life and the effect of periodontal therapy.

2. Can you improve OHRQoL through Periodontal Treatment?

Subgingival debridement (in conjunction with supragingival plaque control) is an effective treatment in reducing probing pocket depth and improving the clinical attachment level (Van der Weijden & Timmerman 2002). However, it is crucial to understand treatment effectiveness from the patient's side (Sischo & Broder 2011) as patient experience is increasingly recognised as one of the three pillars of quality in healthcare alongside clinical effectiveness and patient safety (WHO Working group 1989, Institute of Medicine 2001). This entails a number of dimensions varying from pain and staff empathy to the overall financial costs of treatment.

Quality of life can be positively increased after periodontal treatment (Figure 2). The evidence showed that the vast majority of the studies indicated a significant improvement in OHRQoL after periodontal therapy (Shanbhag et al. 2012). The benefits are clearly noticed after non-surgical periodontal therapy. No differences were noted in terms of type of non-surgical treatment delivery (i.e. lasers, curette, etc.).

Santuchi et al., in 2016, compared scaling and root planing (SRP) per quadrant and one-stage full-mouth disinfection (FMD), on clinical periodontal parameters and OHRQL of patients with chronic periodontitis (Santuchi et al. 2016). 90 patients, divided in two groups, completed both the Oral Impacts on Daily Performance (OIDP) and the Oral Health and Quality of Life (OHQoL): these questionnaires were answered before, and 30 and 180 days after non-surgical periodontal therapy. Clinical periodontal parameters and OHRQL increased after treatment, but no significant differences were found between the two treatment groups.

Interestingly, surgical treatment had relatively low or no impact on OHRQoL if subjects had already received non-surgical therapy (Shanbhag et al. 2012). The reasons for this may be only speculated: it might be that symptoms are mainly dealt with during the healing of the non-surgical treatment and thus reduction of OHRQoL-factors such as halitosis, soreness, bleeding and periodontal pockets are usually solved in terms of self-perception. Muco-gingival surgery, altering recessions in the anterior teeth, might well have an impact on OHRQoL as shown by the patient's satisfaction after treatments (Zucchelli et al. 2012, Cairo et al. 2016).

OHRQoL is surely improved after treatment, as witnessed by the significant changes measured by the questionnaires used. Nevertheless, it is important to understand whether the improvement assessed is clinically meaningful (Jönsson & Öhrn 2014). The issue of the sensitivity of these questionnaires has been thoroughly assessed by Tsakos and co-workers, indicating that mean reduction of the extent (the crude sum of all the answers to the questionnaires) may not represent a real change even if statistically significant (Tsakos et al. 2010). In order to overcome this caveat, the minimally important difference (MID) is to be assessed: MID is the smallest score or change in a score that would be important from the patient's or clinician's perspective. MID has been measured for the ODIP questionnaires in periodontal patients (Tsakos et al. 2010).

3. May improvements in quality of life be maintained over time?
Preventive instruments and supportive periodontal therapies are important tools for the maintenance of a healthy periodontal status. Nevertheless, supportive periodontal treatment is also capable of maintaining a positive evaluation of quality of life. Supportive periodontal therapy is important to maintain over time not only clinical periodontal parameters, but also patients' perception of improvement. Interestingly, subjects undergoing supportive periodontal therapy for a time span inferior to three years show higher level of appreciation of the treatment and higher level of impact on their appearance than subjects with longer supportive treatment (Franke et al. 2015).

SUMMARY

- The addition of OHRQoL to clinical periodontal parameters allows investigating the complete state of physical, mental and social well-being and not just the absence/presence of disease.
- A poor quality of life predisposes the individual to high-risk behaviours such as smoking, alcohol excess, and reduced personal care and hygiene. All these factors contribute to periodontitis.
- Periodontitis-affected subjects show a dose-dependent impairment of quality of life. The severity of periodontitis is directly linked to poor quality of life: most of the periodontal patients' complaints are related to missing teeth and gingival recession, followed by bleeding gums, bad breath, pain/sensitivity and mobility. All these factors influence function, psychological aspects, social perception, oral health, treatment expectations and environment, reducing the quality of life of patients. Periodontal disease is able to influence emotional status such as mood and happiness, reducing smiling patterns.
- Periodontal treatment is capable of improving the quality of life of patients. These effects are mainly related to non-surgical treatment, irrespective of the method of delivery/instruments used. Interestingly, surgical treatment does not add any beneficial effect in subjects that have been already treated non-surgically.
- Supportive periodontal therapy is needed to maintain over time not only clinical periodontal parameters but also patients' perception of improvement.

IMPLICATIONS FOR ACTION

FOR DENTISTS, FOR MEDICAL DOCTORS, FOR THE POPULATION.
An important relationship exists between quality of life and periodontal health status. Quality-of-life measurements investigate function, psychological aspects, social perception, oral health, treatment expectations and environment. The use of these tools in the clinical practice may enhance communication and therefore clinical effectiveness.

A poor quality of life is associated with more severe form of periodontitis and with the poorest treatment outcomes. Periodontal treatment is related to an increase of quality of life, as reported by patients. Dental professionals should be sensitive to their individual patients' needs and ensure that proper and clear information is given about oral conditions and about treatment to enhance patients' feelings of control over the situation. Patients appreciate characteristics that may be related to the so-called "soft skills", such as attitude, attention and capability to explain (Cornwell & Goodrich 2009, Entwistle & Watt 2013).These are essential factors in managing periodontal patients considering that we do not treat millimetres but people.

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Escribano M, Herrera D, Morante S, Teughels W, Quirynen M, Sanz M. (2010) Efficacy of a low-concentration chlorhexidine mouth rinse in non-compliant periodontitis patients attending a supportive periodontal care programme: a randomized clinical trial. *Journal of Clinical Periodontology* **37**, 266–275.

'Efficacy of a low-concentration chlorhexidine mouth rinse in non-compliant periodontitis patients attending a supportive periodontal care programme: a randomized clinical trial'.

INTRODUCTION

Plaque control on the part of the patient is very important for achieving the best results in periodontal therapy. The use of chemical agents helps improve plaque control and reduce gingival inflammation. Chlorhexidine (CHX) is considered to be the "gold standard" of oral antiseptics because of the superiority of its clinical and microbiological effects. The main inconvenience of using CHX in the longer term are its adverse effects: dental staining, burning sensation, and irritation of the soft tissue. To reduce the adverse effects during prolonged use, it has been proposed to reduce its concentration to 0,05% and to combine it with another antimicrobial agent such as cetylpiridinium chloride (CPC).

AIM

To evaluate the clinical and microbiological efficacy of a new mouth-rinse formula with a combination of CHX in low concentration (0.05%) and CPC (0.05%) over three months in patients in periodontal maintenance and with inadequate plaque control.

MATERIAL AND METHODS

Randomized, double-blind, and placebo-controlled clinical study over three months. It included 47 patients which moderate or severe chronic periodontitis in TPA with inadequate plaque control (Turesky index > 1). After the taking of microbiological samples, supragingival prophylaxis, and reinforcement of oral hygiene, participants performed mouth rinses twice daily for three months with the experimental solution (Perio•Aid® 0,05 Dentaid) or the placebo solution (30 seconds with 15 ml of the product), together with normal oral hygiene. In the final visit, the same clinical parameters were registered and microbiological samples were obtained, and the degree of satisfaction with the use of the product was also evaluated. The main criteria for clinical evaluation were the plaque index (PI) and the gingival index (GI). As secondary evaluation criteria, several variables were studied, both periodontal (probing depth, gingival retraction, bleeding on probing) and microbiological.

RESULTS

The plaque-index values were significantly greater in the placebo group compared with the test group after 3 months (3.03 compared with 2.10; $p<0.001$). In terms of the gingival index, the experimental group presented values lower than the control group (0.46 compared with 0.56). A significant reduction in bleeding on probing was observed in the experimental group, while the control group had lower variations. After 3 months, significant reductions in *F. nucleatum* and *P. intermedia* and a reduction in the total bacterial count in saliva was observed in the experimental group.

CONCLUSION

The experimental mouth rinse showed efficacy in reducing the levels of plaque and gingivitis, and in reducing the microbial load in the gingival sulcus, in a group of patients in periodontal maintenance and with inadequate plaque control.

THREE-YEAR RANDOMIZED STUDY OF MANUAL AND POWER TOOTHBRUSH EFFECTS ON PRE-EXISTING GINGIVAL RECESSION.

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INTRODUCTION

The greater efficacy of tooth-brushing with an electrical oscillating-rotating tooth brush has been demonstrated in many publications. The present study provides evidence that, as well as efficacy, this technology is totally respectful of the patient's gingival anatomy.

The aetiology of gingival recession is still not completely understood. It is generally attributed to an accumulation of factors among which anatomical, pathological, and physiological constraints stand out. A recent study of more than 2,000 adults identified as factors recession-causing factors the presence of plaque, gingivitis, sex, age, and smoking habits (Sarfati et al, 2010).

On the other hand, Tezel et al (2001) identified horizontal movements during brushing as the main cause of vestibular gingival recession.

AIMS

To compare the long-term effects of brushing with oscillating-rotating technology compared to brushing with a conventional manual tooth brush on pre-existing gingival recession. After a preliminary publication at 6 months of monitoring (Doerfer et al, 2009), the subjects continued the study with six-month evaluations until 3 years.

MATERIAL AND METHOD

In this controlled, prospective, and parallel-group study, with the examiner of the patients not knowing who belonged to each group, 55 healthy subjects using electric oscillating-rotating-pulsing tooth brushes and another 54 users of conventional manual toothbrushes were monitored over a period of three years. All of them presented recession in the vestibular surface in two or more teeth and of at least 2mm in depth.

All participants were given the instruction to brush twice a day for two minutes using a conventional fluoride toothpaste.

During the study the loss of clinical insertion and depth of probing at 6 points per teeth were evaluated. All the measurements, carefully calibrated, were performed by the same examiner. Gingival recession was calculated as the difference between the loss of clinical insertion and the depth of probing.

Soft and hard tissues were also evaluated to evaluate the control of the study.

RESULTS

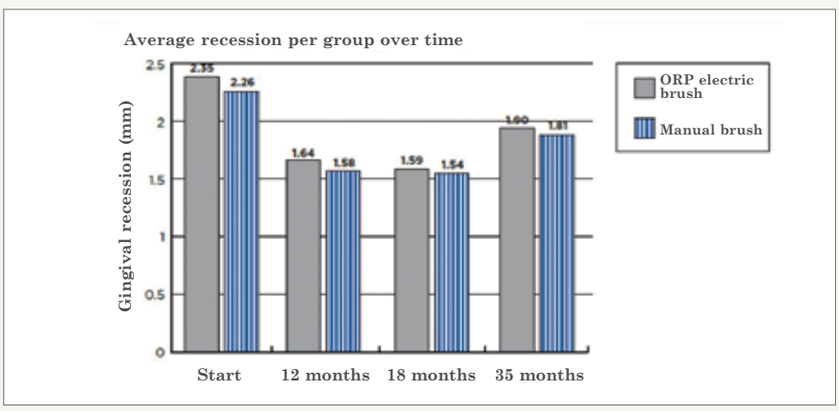
After 35 ±2 months, average gingival recession was not significantly different between the two groups, although there was a significant difference from the initial values ($p<0,001$). This ranged from 2,35 ±0,35mm to 1.9 ±0,58 mm in the study group with electric toothbrushes, and from 2,26 ±0,31mm to 1,81 ±0,66mm in the manual-brushing group.

DISCUSSION

An unexpected finding of this study was the significant reduction in pre-existing recession over time in both groups. Even though after 12 months a slight tendency to relapse appeared, after 3 years the recessions showed a better condition than at the start. This is the first study to show that localised recessions can be improved when attention is paid to tooth-brushing technique. Despite this, there is a multitude of studies which show that a lack of care in the technique of manual brushing (too much pressure, horizontal movements) will have a negative effect on gingival anatomy. On the other hand, there also exists valuable evidence that brushing with oscillating-rotating-pulsing technology with pressure control offers better plaque removal than manual brushing.

CONCLUSIONS

Gingival recession in subjects with existing lesion reduced in a significant way after 3 years of brushing with a manual tooth brush or an electric oscillating-rotating-pulsing brush with pressure control.



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ISDIN

EFFICACY OF CHLORHEXIDINE, DEXPANTHENOL, ALLANTOIN AND CHITOSAN GEL IN COMPARISON WITH BICARBONATE ORAL RINSE IN CONTROLLING POST-INTERVENTIONAL INFLAMMATION, PAIN AND CICATRIZATION IN SUBJECTS UNDERGOING DENTAL SURGERY.

REFERENCE

Lopez-Lopez J, Jan-Pallí E, lez-Navarro BG, Jané-Salas E, Estrugo-Devesa A, Milani M. (2015) Efficacy of chlorhexidine, dexpanthenol, allantoin and chitosan gel in comparison with bicarbonate oral rinse in controlling postinterventional inflammation, pain and cicatrization in subjects undergoing dental surgery. *Current Medical Research and Opinion* **31**, 2179-83.

The reduction of inflammation and pain after interventions of dental-surgery procedures, such as extraction of teeth, implants, or oral biopsies is an important clinical objective.

Lopez-Lopez et al evaluated the efficacy of dental gel (DG) to evaluate the degree of control of inflammation, pain, and cicatrization after the extraction of molars.

MATERIAL AND METHODS

A prospective, crossover, sequential, controlled, and randomized study in patients submitted to surgery of at least two-thirds impacted mandibular molars, in two separate sessions, to determine the effect of dental gel (GD) in comparison with a bicarbonate oral rinse (BC), both used three times a day. In a random and sequential manner, each subject used both products after each dental extraction. Pain six hours after the dental extraction and on six successive days, inflammation by means of facial perimeter, the use of painkillers, and cicatrization by means of a semi-quantitative scale were all evaluated.

RESULTS

A total of 47 patients were included from whom 94 molars were extracted. As the first sequential treatment 19 BC/ 28 DG were used. After surgery, no significant differences were noted in terms of inflammation. At six hours, the quantification of pain using VAS was 6.5, similar in both treatments. The subjects who used DG maintained a marked and progressive reduction in the intensity of pain during the 7 days after the intervention (3.7 vs 5.3; $p = 0{,}0001$). DG was superior to BC in terms of: reducing inflammation (6 mm compared with 12 mm, $p = 0{,}0001$), the consumption of painkillers (13 tablets vs 24; $p < 0{,}05$), "good" cicatrization (64% vs 13%; $p = 0{,}0001$). No serious side-effects were reported with either of the treatment regimens.

CONCLUSION

In this study, dental gel had better results than bicarbonate oral rise in the control of pain and inflation in subjects submitted to dental surgery, and also reduced the consumption of painkillers and favoured a better cicatrization.

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TREATMENT OF SEVERE MUCOGINGIVAL DEFECTS WITH COMBINATION OF CONNECTIVE–TISSUE GRAFTS AND COLLAGEN MATRICES.

REFERENCE

Urban IA, Lozada JL, Nagy K, Sanz M. (2015) Treatment of severe mucogingival defects with a combination of strip gingival grafts and a xenogeneic collagen matrix: a prospective case series study. *International Journal of Periodontics & Restorative Dentistry* **35**, 345-53.

INTRODUCTION

There are clinical situations in which the increase in soft tissue through techniques of mucogingival surgery is indicated. To achieve the most stable results we resort to soft-tissue grafts. However, this brings with it morbidity for the patients, especially when a wide zone is regenerated. Recently, the xenograft, using a collagen matrix, has been presented as a substitute for soft tissue to gain keratinised tissue around teeth and implants. Nonetheless, knowledge about its indication in extensive mucogingival defects is still limited.

AIM

This prospective case study evaluates the results obtained using a combined technique of free gingival graft in a strip and a collagen matrix to restore severe mucogingival alterations.

MATERIAL AND METHODS

Twenty patients were included who presented an area with an absence of keratinised tissue and a loss of vestibular height, associated with techniques of vertical and horizontal ridge augmentation. All had good periodontal and systemic health and were non-smokers.

The "combined graft technique" was evaluated: positioning a strip of autogenous free gingival tissue, apically, together with a collagen matrix (Geistlich Mucograft®). Horizontal incisions were made in the keratinised tissue parallel to the mucogingival junction. A flap of partial thickness was raised to reposition the mucogingival line apically and it was sutured with 5-0 suture (Monocryl, Ethicon). An autogenous graft of gingival tissue free of palatal mucosa, of 2 to 3 mm in width and 1.5 mm in depth (graft in strip) was obtained, and was immediately sutured at the apical margin of the recipient bed with monofilament suture (6.0 PDS-II, Ethicon). The rest of the recipient bed was covered with Geistlich Mucograft®, cut to the dimensions of the bed and sutured in the same way, and left exposed. The patients received instructions on mouth-rinsing with chlorhexidine 0.2%, systemic anti-inflammatory medication, and were evaluated 7 and 14 days after surgery.

The changes in the width of keratinised gum were evaluated at 1, 3, 6, 9 and 12 months. In addition, the degree of contraction of the graft and the morbidity of the patient in the first and second weeks after the surgery was evaluated.

RESULTS

The 20 patients completed the evaluation 12 months after surgery. Of the surgeries, 85% were carried out in the maxilla, nine in the posterior zone and eight in the anterior. Two surgeries were performed in the jaw, one in the anterior sector and one in the posterior sector.

None of the patients suffered post-operatory complications of relevance. After the first week, the grafted zone showed good conditions of cicatrization. All the treated zones presented a significant increase in keratinised gums, with an average gain of 6.33 mm at 12 months (SD: 2.16 mm; 95% CI: 5.31-7.34) and contraction of the graft of 43% (SD: 11.0%; 95% CI: 37.9-48.42). Clinically, the regenerated soft tissue presented an aspect of health and colour coinciding with the neighbouring zones, except in the area of autograft, where there was an appreciable alteration in consistency and colour.

The majority of patients reported moderate pain in the treated zone, 10 patients did not require medication during the first week, and none after that.

DISCUSSION

This study shows that the combination of a collagen matrix and a graft of free autogenous gingival tissue in strip can be used in a safe way to restore severe mucogingival defects. Relevant clinical studies conclude that a greater zone of keratinised tissue preserves the long-term stability of soft and hard tissue around implants.

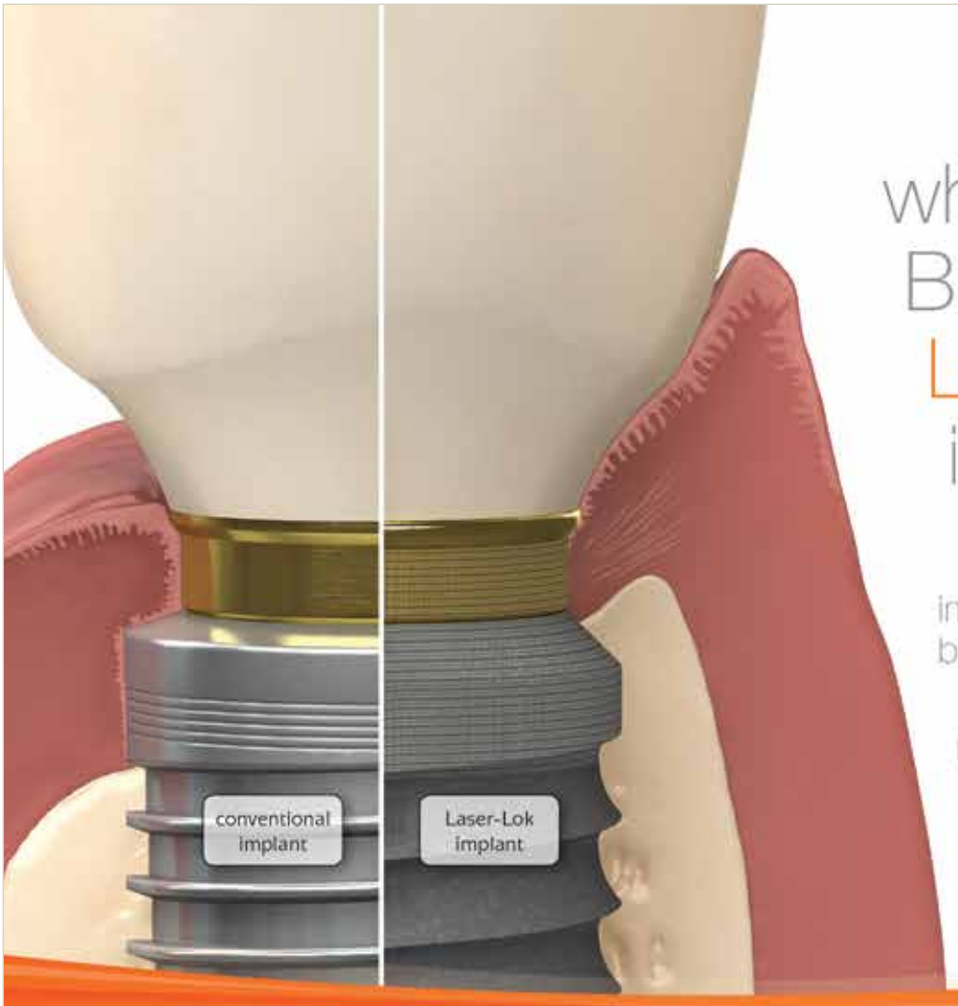
Comparative studies demonstrate that the free gingival graft produces less contraction compared to the grafting of free connective tissue. In a recent systematic study, collagen matrices were observed to be capable of successfully increasing the keratinised tissue. In this study, the technique of combined grafting showed a significant gain in keratinised gum and a lesser contraction to that previously reported.

The collagen matrix stabilises blood clotting, providing a scaffold where the cells and blood vessels of adjacent tissues migrate to form keratinised tissue, while the graft in strips would act as a barrier to the alveolar mucosa. This xenogeneic matrix has shown great biocompatibility and porosity with the absence of inflammatory reaction.

The use of the combination of grafts has been well accepted by patients, with minimal comorbidities. All this means that this technique is simpler and more advantageous when compared to others, obtaining the autogenous graft in strips and its positioning is not difficult, and the collagen matrix has an excellent handling.

CONCLUSION

The combination of a xenogeneic collagen matrix (Geistlich Mucograft®) and a free gingival tissue graft in strips is safe and efficient in the regeneration of extensive mucogingival defects. The positive results need to be evaluated and validated by controlled clinical studies.



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2. S Botos et al. *Int J Oral Maxillofac Implants*. 2011; 26:492-498.
SPMP16251 REV A AUG 2016

RANDOM DOUBLE-BLIND STUDY COMPARING IMPLANTS WITH COLLAR SURFACE MICROTEXTURED BY LASER AND IMPLANTS WITH MACHINED SURFACE. MICROBIOLOGICAL AND CLINICAL RESULTS.

REFERENCE

Guarnieri R, Rappelli G, Piemontese M, Procaccini M, Quaranta A. (2016) A Double-Blind Randomized Trial Comparing Implants with Laser-Microtextured and Machined Collar Surfaces: Microbiologic and Clinical Results. *International Journal of Oral & Maxillofacial Implants* **31**, 1117-25

AIM

The aim of this study was to compare the clinical results and determine the differences in the periodontal-pathogenic microbiota around two types of surfaces in the collar of implants: microtextured with laser (test) vs machined (control).

MATERIALS AND METHODS

Seventeen patients (11 periodontally healthy and 6 periodontally compromised) were selected to each receive two different implants, randomly selected, in two places with missing teeth. Six months after the surgical placement of the dental implants, samples of subgingival plaque of the peri-implant sulcus and the sulcus of the adjacent tooth were collected with paper points. The presence of five putative periodontal pathogens – namely, *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, and Tannerella forsythensis* – was evaluated by means of real-time polymerase chain reaction (RT-PCR). The peri-implant parameters and the intraoral radiographs were registered until one year after the connection of the abutment.

RESULTS

In the main population and in the periodontally compromised subgroup, the total number of periodontal pathogens around the test implants was less than in the control implants and adjacent sites, with a statistically significant difference ($p < 0.05$). In the periodontally heathy patients, the average depth of probing for the test implant was 1.31 ± 0.51 mm, compared with 2.66 ± 0.83 mm for the control implant, while in the periodontally compromised patients it was 1.61 ± 0.58 mm for the test implant compared with an average value of $2.84 \pm 1{,}0$ mm for the control implant.

DISCUSSION

The present study compares the microbiological differences in partially edentulous patients between two implants currently available commercially: Tapered Internal from BioHorizons, mount-free with a surface in the implant collar microtextured by laser (test), and a Tapered Internal from BioHorizons, mount-free with a mechanised surface in the implant collar. In the periodontally compromised subgroup it was found that the concentration of specific periodontal pathogens was lower around the test implants than the control implants and the adjacent sites. In the presence of adjacent teeth affected by periodontal disease, a microtextured surface, in comparison with a mechanised surface, appears to promote the formation of a greater support for soft tissues in the transmucosal area. Important limitations of this study are its small size and the short monitoring period. As a result, final confirmation of the findings requires additional studies with longer periods of observation and with a larger number of implants.

CONCLUSION

Implants with a collar surface microtextured by laser are not more vulnerable to colonization by pathogenic microflora than implants with a machined collar surface. In the two patient subgroups (periodontally healthy and periodontally compromised), the implants with a collar surface microtextured by laser have a better clinical result a year after loading, in comparison with implants with a machined collar surface

SEPA

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The Alianza por la Salud (Alliance for Health) is a project driven by the **SEPA Foundation** which promotes the relationship between periodontal and general health. It is aimed at the public, at patients, and at all health professionals. It is a scientific and educational co-operation initiative which results from the working groups of the **Spanish Society of Periodontology** (SEPA), the **Spanish Society of Diabetes** (SED), with the support of the **Society of Gynaecology and Obstetrics** (SEGO), the **Society of Primary Care Doctors** (SEMERGEN), and the **European Federation of Periodontology** (EFP).

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SEPA expresses its thanks for the support of the businesses that collaborate in the development of the working groups and in driving the Alliance for Periodontal and General Health

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ALLIANCE FOR PERIODONTAL AND GENERAL HEALTH.

WHAT IS THE ALLIANCE FOR PERIODONTAL AND GENERAL HEALTH?

IT IS A JOINT INITIATIVE for promoting periodontal and general health, driven by the **Fundación SEPA de Periodoncia e Implantes Dentales [SEPA Foundation of Periodontology and Dental Imolants]**, supported and developed by the **Sociedad Española de Cardiología [Spanish Society of Cardiology]** (SEC), and the **Sociedad Española de Diabetes** [Spanish Society of Diabetes] (SED).

WHO IS INVOLVED IN THIS ALLIANCE FOR PERIODONTAL AND GENERAL HEALTH?

AS WELL AS SEC, SED, AND SEPA, all institutions, associations, interest groups, health professionals, and scientific entities which place the health and well-being of people as the centre of their activity are invited to join this open co-operation initiative.

WHY IS AN ALLIANCE FOR HEALTH NEEDED?

IN 2013, THE EUROPEAN FEDERATION OF PERIODONTOLOGY (EFP), with the support of SEPA, prepared and distributed the Manifesto "Perio and General Health": a call to the oral-health community and to health professionals which sought to strengthen the prevention and early diagnosis of periodontal diseases and their treatment, avoiding their potential consequences for general health.

The points expressed in this Manifesto stem from the conclusions of the 9th European Workshop in Periodontology held in November 2012 in Spain (in the Granja de San Ildefonso, Segovia) where 90 experts from the European Federation of Periodontology and the American Academy of Periodontology, under the direction of Mariano Sanz, chair of periodontology at the Complutense University of Madrid, came together to address the association between gum diseases and general health.

A consensus was reached that periodontal diseases should be recognised as an important matter of public health given their high prevalence (in Spain, eight out of 10 Spaniards over 25 suffer from gum diseases) and that, as a result, dentists and health professionals should be provided with guidelines about diagnosis and treatment, as well as studies that identify the consequences of these associations.

These are the main findings/conclusions of the 9th European Workshop:

1. That there is a wealth of scientific evidence which links periodontitis – wrongly called pyorrhoea – with the discompensation of diabetes, cardiovascular diseases, and adverse outcomes during pregnacy, and this evidence has to be brought to the attention of the population.
2. That the care of patients' health requires multidisciplinary perspectives between dentists and other health professionals such as endocrinologists, cardiologists, gynaecologists, and primary-care doctors.
3. That future research in periodontology should consider specific objectives in the field of diabetes, cardiovascular disease, alterations during pregnancy, and other systemic conditions.
4. That there is a need for collaboration between different interest groups, including: periodontists (dentists specialised in gums), general dentists, hygienists, scientific dental societies, professional colleges of dentists and associations/ colleges of dental hygienists; cardiologists, endocrinologists, gynaecologists, and obstetricians; primary-care doctors and all personnel linked to these disciplines: nurses, midwives, and educators, among others. Universities, research centres, businesses in the oral and pharmaceutical sector, patients, communications media, and public institutions.

WHAT DOES THE ALLIANCE FOR PERIODONTAL AND GENERAL HEALTH ENTAIL? ACTIONS

TO ACHIEVE THE MAXIMUM CONSOLIDATION of this initiative, the Alliance for Health invites all working groups, professionals, and member entities to propose actions focused on these three lines of action:

1. **Information:** the wealth of available scientific evidence must be brought to the attention of professionals and the population.

It is necessary to train health professionals and inform patients of the benefits of good oral and periodontal health in relation to their diabetes (*Herrera et al. 2014*). Accordingly, there are recommendations for doctors and health personnel who serve people with diabetes; for dentists and oral-health teams; and for patients, both in the dental clinic and the doctor's surgery; proposed in the EFP-AAP Workshop (*Chapple et al. 2013*) and which SEPA has adapted and made available to the different interest groups.

Doctors must be aware of the emerging evidence for the strengthening of periodontitis as a risk factor for the developent of atherosclerotic cardiovascular disease and advise patients of the risk of periodontal inflammation to general health, as well as to oral health (*Tonetti et al. 2013*).

2. **Multidisciplinary integration:** centred on patient care.

Oral and periodontal health should be an integral part of the management of diabetes (*Herrera et al. 2014*).

Collaboration between professionals of medicine and dentistry is becoming more and more important (*Herrera et al. 2014*):

The dental clinic can serve to detect people at risk of suffering diabetes. Medical staff, involved in the care of diabetes patients, can collaborate in the prevention and early diagnosis of periodontal pathologies.

Caring for periodontal health is important in the care of the cardiovascular patient and screening for periodontal disease should be included within the protocols for cardiological care. For those cases in which the clinical diagnosis of the patient is not possible, various systems of monotiring based on questionnaires are proposed (*Noguerol et al. 2015*).

The accumulated evidence sustains the idea that ischemic cardiovascular disease, diabetes, and periodontitis share common risk factors, but, in turn, can behave mutually as aggravating factors of the others. For this reason, there is a need for combined actions dedicated to prevention and treatment, trusting that in this way we can improve general and oral health (*Noguerol et al. 2015*).

The dentist has the responsibility for detecting individuals with metabolic and/or cardiovascular risk, sending them for medical attention and advising their patients about health-promotion strategies (*Noguerol et al. 2015*). Based on the weight of evidence, periodontal patients with other risk factors for atherosclerotic cardiovascular disease, such as hypertension, overweight/obesity, smoking, etc., who have not visited a doctor during the previous year, must be referred to a medical examination (*Tonetti et al. 2013*).

The risk factors for periodontitis and cardiovascular disease, modifiable and associated with lifestyle, should be tackled in the dental appointment and in the context of integral periodontal therapy, which is to say, in programmes for smoking cessation and assessments of lifestyle modifications (diet and exercise). The task can be achieved in collaboration with appropriate specialists and can deliver health benefits (*Tonetti et al. 2013*).

3. **Research:** focused on contributions such as the response of other disciplines, the development of combined protocols and clinical guides, and their corresponding validation.

PREDAPS study. The assessment of periodontal health through a questionnaire has been included in the prospective study of prediabetes in Spain (PREDAPS), organised by the Red de Grupos de Estudio de la Diabetes en Atención Primaria de la Salud [Networks of Study Groups of Diabetes in Primary Healthcare] (redGDPS), whose objective is to determine the risk of diabetes and vascular complications in prediabetic patients.

Di@bet.es study. About the incidence of Type 2 diabetes in Spain and associated risk factors, organised by the Centro de Investigación Biomédica en Red [Centre of Biomedical Research in Network] (CIBER). This study will include the assessment of periodontal health through a questionnaire and, in some centres, evaluation with clinical examination to validate it.

Estudio DiabetRisk. SEPA's network of research clinics (Red de Clínicas de Investigación de la Sociedad Española de Periodoncia) has started an ambitious and innovative project, with the aim of evaluating, in a situation of real clinical practice, the efficacy in the dental consultation of an evaluation protocol of the risk of undiagnosed diabetes or prediabetes. The study, designed by the Aetiology and Therapy of Periodontal Diseases (ETEP) research group at the Complutense University, has been supported by the working group "Diabetes and Periodontal Disease", made up of experts from the Spanish Society of Diabetes (SED) and the Spanish Society of Periodontology (SEPA). In addition, the study has now received approval from the ethical committee of the Hospital Clínico de Madrid, and it is expected to start in June 2017

Development of joint protocols and clinical guides:

There are recommendations about the association between diabetes and periodontitis (for doctors and health staff who treat people with diabetes, for dentists and the oral-health team, and for patients, both at the dental clinic and the doctor's surgery), proposed in the joint EFP-AAP Workshop (*Chapple et al. 2013*) and which SEPA has adapted and made available for the different interest groups.

Scientific and professional bodies have highlighted the impact of the relationship between periodontal diseases and acute myocardial infarction, and the need to undertake actions for the prevention of both pathologies. These actions should involve cardiologists and dentists equally, and should generate joint protocols for action to achieve this end. There is a lack of specific action protocols with operational targets for both groups (*Noguerol et al. 2015*).

GLOBAL OBJECTIVE: HEALTHCARE INTERVENTION AND BENEFITS TO PUBLIC HEALTH

As well as strengthening information, the multidisciplinary relationship, and research, the Alliance for Health promotes active strategies of health promotion, involving the patient, from a twin perspective:

1. Through an appropriate training and qualification of dentists and dental hygienists to strengthen their skills and ensure that the dental clinic is a space for the primary prevention of non-communicable diseases, especially cardiovascular and diabetes, the fight against smoking, and the promotion of healthy lifestyle habits.
2. Integrating the promotion of periodontal health into their service portfolio, at least, in specific population groups: patients with diabetes, patients with cardiovascular diseases, and pregnant women.

With this double aim, SEPA/Alliance for Health takes on a scientific and educational leadership shared with scientific societies to ensure that a paradigm shift among oral-health professionals will take place in the coming years and will be translated into specific action programmes.

Over the coming years, to develop and put into practice the initiative described in this document, SEPA, together with other scientific societies, entities and businesses committed to science and health, will deploy intervention strategies and health targets in the following work programmes:

- Prevention, early diagnosis, and correct treatment of periodontal diseases.
- Prevention, early diagnosis, and correct treatment of peri-implant diseases.
- Primary prevention of cardiovascular pathologies through the Mimocardio network of clinics. Cuida tus Encías [Take care of your gums].
- Integration of intervention protocols that allow the early detection of undiagnosed diabetes patients in the dental consultation.
- Integration of effective intervention protocols that allow a contribution to eradicating tobacco addiction.
- Promoting women's oral health and preventive habits throughout life.
- Special emphasis on preventing obesity and alcoholism.

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THE BENEFITS OF PERIODONTAL HEALTH: ORAL HEALTH AND BEYOND...

DAVID HERRERA & PHOEBUS MADIANOS, GUEST EDITORS OF PERIODONCIA CLÍNICA Nº 8

THE PRESENT ISSUE of *Periodoncia Clínica* is entitled "The systemic benefits of periodontal health". When the theme of the issue was discussed, it was felt that there was a timely need to bring forward to the dental community the current state of knowledge on this rapidly growing and important topic. Clinicians are very aware of the significant oral benefits of periodontal health (and periodontal therapy), based on their own experience and on a vast amount of existing scientific evidence: teeth are maintained in function on a long-term basis, no bleeding, no tooth mobility, less risk of halitosis… However, in the last years, scientific evidence has also provided solid basis for potential benefits beyond the oral cavity.

To address this topic, relevant researchers from all over the world were contacted and agreed to summarize the current knowledge, presenting the epidemiological data, describing the underlying biological mechanisms and, more importantly, appraising the expected benefits of periodontal health/therapy in the particular systemic disease of their expertise.

The list of authors includes some of the most important researchers in the field and the centres involved cover a wide range of the most prestigious research laboratories and clinics, from six different countries in two continents: The universities of Groningen and Amsterdam & Vrije Universiteit Amsterdam (The Netherlands), Bristol, Birmingham and University College London (UK), Athens (Greece), Pisa (Italy), North Carolina (Chapel Hill, USA), and University Complutense (Spain).

When exploring the relevant conditions which should be addressed, the invited editors selected seven, among the "57 distinct and unique systemic conditions" that have been researched in relation to periodontitis (Monsarrat et al. 2016): extraoral infections caused by oral pathogens, Alzheimer´s disease, rheumatoid arthritis, diabetes, perinatal complications, erectile dysfunction and cardiovascular diseases. In addition, the influence of periodontal health/therapy on overall quality of life was identified as an important aspect of both oral and systemic benefits.

- Van Winkelhoff, Abbas and Siebers conclude that "maintaining good oral health not only benefits the dentition but also general health", since extra-oral infections of oral origin might cause life-threatening diseases (van Winkelhoff et al. 2017).
- Barros, Aoyama, Moy and Offenbacher describe "an association between poor oral health and adverse pregnancy outcomes such as preterm birth, low birth weight and pre-eclampsia", however, periodontal treatment (which has been shown to be safe for the pregnant woman and her child) during pregnancy does not seem to improve pregnancy outcomes (Barros et al. 2017).
- In our own paper (Montero et al. 2017), the better control of hyperglycaemia, observed after non-surgical periodontal therapy, could easily reduced diabetes complications and all-cause mortality.
- Orlandi and D'Aiuto (2017) stress that the current evidence supports the association between periodontitis and cardiovascular diseases and, furthermore, that periodontal treatment can benefit cardiovascular health (using surrogate markers).
- Loos (2017), after evaluating the connexions between periodontitis and erectile dysfunction, suggests that periodontitis screening and periodontal treatment could be helpful in managing this form of impotence.
- West, Shoemark, Davies and Allen-Birt highlight that "if periodontal diseases could be controlled by excellent oral hygiene and regular supportive dental care, teeth could be maintained…possibly Alzheimer's disease may be slowed in the early stages with immense benefit for all" (West et al. 2017).
- López-Oliva, De Pablo, Chapple, Dietrich and Grant point out that "periodontal therapy could be a non-expensive, non-pharmaceutical way of improving rheumatoid arthritis" and that "patients diagnosed with rheumatoid arthritis should be advised to visit their dentist and maintain special care with their periodontal health" (López-Oliva et al. 2017).

- With a different perspective, Graziani, Bettini and Petrini clearly demonstrate that an important relationship exists between quality of life and periodontal health status: a poor quality of life is associated with more severe forms of periodontitis and with poor treatment outcomes, while effective periodontal treatment is related to an increase in quality of life (Graziani et al. 2017).

Taken together, all these findings clearly indicate the next step: it is time to take action. It is mandatory to use the available information for the benefit of our patients as well as for the benefit of the general public. It is not an easy task, but its potential public-health impact justifies the efforts. As some examples, actions may include:

- Promote awareness among health professionals, including general medical and dental practitioners, health authorities, patients and even the general public, on the potential systemic risks associated with periodontal diseases.
- Increase the understanding among dental professionals, based on current evidence, that their task and efforts to promote oral health may award benefits to their patients that exceed the boundaries of their mouth and potentially improve the quality of their life.
- Expand the role of the dentist beyond maintaining dental and oral health, as they may also help in the early detection of relevant systemic conditions, such as diabetes and cardiovascular diseases, especially in patients suffering from periodontitis and presenting with other relevant risk factors. .
- Dentists should also assume an active role in the control of modifiable lifestyle-associated risk factors, which affect both periodontitis and other systemic diseases: i.e. smoking-cessation programmes and advice on lifestyle modifications, including diet and exercise.

periodoncia clínica

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