Chapter

Periodontitis and Heart Disease: Current Perspectives on the Associative Relationships and Preventive Impact

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Abstract

Due to the important advancement and the accumulation of new evidence on the periodontitis-cardiovascular disease (CVD) relationship as well as the major medical, economic and social burden caused by both diseases this chapter aims to review existing epidemiological and pathogenetic links related to this topic. Also, this chapter aims to highlight the impact of the periodontitis-CVD relationships on clinical practice and on the preventive approaches targeting to decrease the impact of periodontitis on CVD. Periodontitis is an infectious disease eliciting local and general inflammation, which leads to periodontal destruction and systemic involvement. Several pathways could explain the link between periodontitis and CVD such as bacteraemia, chronic persistent systemic inflammation and oxidative stress. The first step in the treatment of periodontitis addresses the elimination of microbial components, which lead to a decrease in local and systemic inflammation. Periodontal therapy seems to positively impact CVD. Specialists should inform patients with CVD on the negative impact of periodontitis on their systemic status and refer patients to the periodontist for an extensive examination as routine management of CVD. Some possible risks of periodontal therapy should be considered in patients undergoing antithrombotic medication.

Keywords: periodontitis, cardiovascular disease, atherosclerosis, hypertension, inflammation, anticoagulants, prevention

1. Introduction

Periodontitis is a noncommunicable infectious disease associated with an important inflammatory component affecting around 50% of the population worldwide and with a prevalence of its severe forms of 11.2% [1]. The Global Burden of Diseases, Injuries, and Risk Factors Study (2017) reported periodontitis as the sixth most prevalent chronic human disease [2].

Periodontitis is characterized by loss of connective tissue attachment that is normally located at the tooth neck (cementoenamel junction) as well as by alveolar bone destruction. Periodontitis is accompanied by the transformation of the shallow gingival sulcus into a deep periodontal pocket and a marked apical diffusion of the dysbiotic subgingival biofilm [3]. In generalized severe periodontitis, the surface area of the epithelial lining of the periodontal pockets is enormous and could favor the direct contact of subgingival bacteria with gingival connective tissue through focal ulcerated areas. Moreover, epithelial ulcerations constitute biological entries for the systemic dissemination of subgingival Gram-negative bacteria and local products eliciting different general biological responses [3, 4].

There is important evidence suggesting periodontitis as a biologically plausible risk factor for the development of other chronic, systemic, inflammatory conditions such as diabetes mellitus, cardiovascular disease (CVD), and adverse pregnancy outcomes [5]. Relationships between periodontitis and chronic obstructive pulmonary disease, rheumatoid arthritis, metabolic syndrome, obesity, cancers, and chronic renal disease have also been reported [6]. An inverse influence of systemic conditions on periodontal status has also been described [7]. Current epidemiological evidence sustains that periodontitis induces an increased risk for future atherosclerotic CVD [8].

The term CVD refers to atherosclerotic conditions such as coronary heart disease, cerebrovascular disease and peripheral vascular disease representing a leading cause of death, impairments, and quality of life alterations [8]. CVDs are the most prevalent noncommunicable diseases globally due to the increasingly aging population as well as to profound alterations of diets and lifestyles. Eurostat, the statistical office of the European Union, reported that in 2016 in UE 1.68 million deaths were resulting from diseases of the circulatory system, which was equivalent to 37.1% of all deaths—considerably higher than the second most prevalent cause of death, cancer (malignant neoplasms 25.8%). They accounted for 50–60% of all deaths in the Baltic Member States and Romania and 65.8% of all deaths in Bulgaria. By contrast, less than one-quarter of all deaths in Denmark (22.6%), France (24.3% 2016 data) and the Netherlands (25.0%) were caused by diseases of the circulatory system [9].

Periodontitis has a negative impact on cardiovascular outcomes. Also, periodontal treatment has been associated with potential risks and complications in patients on anti-thrombotic therapy which must be considered in clinical practice [8].

Due to significant advancement and the accumulation of new evidence on periodontitis-CVD relationships as well as to the major medical, economic and social burden represented by both periodontitis and CVD, this chapter aims to review existing epidemiological and pathogenetic links related to this topic as wells to highlight the impact of the periodontitis-CVD associative relationships on clinical practice and to provide some clinical recommendations for both periodontists and cardiologists on this topic.

2. Pathophysiological links between periodontitis and CVD

2.1 Subgingival microbiota and periodontitis development

A highly organized subgingival microbial community is involved in the transition from a periodontal health condition to a dysbiotic pathogenic status namely periodontitis characterized by a complex shift of the microbiota composition, abundance, and arrangement [10, 11]. Three members of the subgingival consortium included in the "Red complex" have been constantly identified in the subgingival microbiota of periodontitis patients are: *Porphyromonas gingivalis* (*P. gingivalis*), *Treponema denticola* (*T. denticola*), and *Tannerella forsythia* (*T. forsythia*) [12]. Previously viewed as true periodontopathogens, they are now rather considered as pathobiont organisms because these bacteria are normally present in low numbers in the subgingival microbiota of periodontal healthy individuals [13]. *Filifacter alocis* and bacteria of genera *Parvimonas, Fusobacterium*, and *Prevotella* are nowadays considered as pathobionts [14]. Pathobionts expand within the microbial community once ecological changes take place, which initiates and favor periodontitis development [11]. Dynamic and synergistic interactions between subgingival microbiota and the host shape and stabilize dysbiotic communities within their subgingival habitat [15]. Gingival inflammation triggers local tissue destruction that releases subgingivally specific nutriments corresponding to the growth of highly demanding Gram-negative bacteria, which amplify local dysbiosis [16].

A paradox remarqued by the specialists is that dysbiotic microbiota requires inflammation to sustain their nutrition in the context in which localized inflammatory reaction developed by the host is a normal function addressed to reestablish local homeostasis through inhibiting bacterial development [11]. The behavior of *P. gingivalis* could explain this paradox through the manipulation of the periodontal immune reactions [17].

A low proportion of *P. gingivalis* in the subgingival microbiota in both periodontal health and periodontitis has been identified. The bacterium is considered a keystone pathogen in the dysbiotic microbiota creating a pro-inflammatory, antiphagocytic environment favorable to the growth and development of pathobionts [18].

Upregulation of many virulence genes of *P. gingivalis* in healthy sites before progression of the attachment loss has been described. In contrast, *T. denticola* and *T. forsythia* upregulate only very few virulence genes and only in the later stages of periodontitis evolution. It seems that *P. gingivalis* serves as a microbial driver in the transition from periodontal healthy status to periodontitis [16].

Microbiota within the subgingival biofilm is a complex highly dynamic architectural arrangement of bacteria rather than a random static positioning of the microbial cells next to each other. Within the biofilm, biochemical interaction, signaling, and genetic exchanges between bacteria take place. Facultative aerobes within subgingival biofilms can sequester oxygen and create anaerobic niches that favor the expansion of anaerobic protobionts and thus the transition toward dysbiosis [11]. The bacterial load in periodontal pockets is exponentially greater compared to the flora of the sulcus at the expense of the dominant species rather than due to the replacement of early colonizers [16]. Four distinct layers have been described in the subgingival biofilm from periodontitis patients. The basal layer of the subgingival biofilm, located in the proximity of the tooth surface, is formed by *Actinomyces* spp. *Fusobacterium* and *Tannerella* reside in the intermediate layers of the biofilms while *Prevotella* and

Porphyromonas are localized in both the apical and intermediate layers [19]. Bacterial cells of the *Cytophaga-Flavobacterium-Bacteroides* cluster were located in the apical layers and *Treponema* was located above the densely packed biofilm. Microbial cells of the genus *Synergistes* have been described closely arranged to polymorphonuclear leukocytes indicating direct physical interactions between biofilm microbes and host immune cells [19]. However, close relationships between polymorphonuclear leucocytes and subgingival microbes have been previously highlighted through transmission electron micrographs [20].

2.2 Pathogenetic mechanisms linking periodontitis and CVD

Atherosclerosis is a chronic, vascular inflammatory condition being a major cause of CVD. In atherosclerosis, the deposition of lipids in the artery walls results in plaque build-up. Its progression results in the reduction of blood flow and consecutive ischemia of organs and tissues and promotes clot formation [21]. The American Heart Association pointed out the relationships between periodontitis and CVD although causality remains unproven [22, 23].

A wide range of studies has investigated the causal relationships between periodontitis and CVD which have resulted in two essential hypotheses explaining this link. One hypothesis sustains the role of systemically disseminated periodontopathogens and of their by-products to induce atheroma formation through the infection of blood vessels [24]. Disseminated bacteria and their products including lipopolysaccharide (LPS) challenge the immune system inducing systemic inflammatory reactions [3].

Several data communicated over time have reported the ability of bacteria from subgingival plaque to migrate and localize to vascular walls and atheromatous plaques. Recent information provided by a systematic review and a meta-analysis showed that the DNA of periodontopathogens was present in atheromatous plaque samples from patients with myocardial infarction [25]. However, less than 5% of patients receiving surgery for atherosclerotic vascular disease presented bacterial DNA in isolated samples which were not statistically significantly different from patients receiving surgeries for rheumatic heart disease [26].

The second hypothesis considers that longstanding periodontal inflammation overlaps with existing chronic systemic inflammation through the dissemination of locally abundantly produced molecules (pro-inflammatory cytokines, chemokines, and gingiva-derived C-reactive protein CRP) promoting atherosclerosis development and CVD [24, 27].

Moreover, a recent emerging hypothesis considers that periodontopathogens and periodontal inflammation promote modifications in oral and gut microbiome which in turn may influence the evolution of both periodontitis and atherosclerosis [24].

In periodontitis patients, the processing of antigenic structures by the liver induces a systemic acute phase response associated with an increased plasma CRP [3]. Periodontitis patients have statistically significantly higher high sensitivity CRP plasma values compared to periodontally healthy subjects amounting to 1.56 mg/L. This difference is biologically relevant since it could drive patients into the high CRP risk category (>3 mg/L) [28]. IgG antibodies against specific periodontal bacteria were associated with all-cause and CVD mortality [29].

A vascular endothelial activation is a central event for atherosclerosis development and a connecting link to periodontitis [30]. Circulating bacterial LPS, outer membrane vesicles and fimbriae, as well as inflammatory cytokines induce the

up-regulation of cell-surface receptors and the expression of adhesion molecules on the vascular endothelium, which recruit peripheral blood monocytes at the surface of the activated endothelium. On the other hand, antibodies targeting specific bacterial proteins behave as auto-antibodies through "molecular mimicry" and induce damage of the vascular endothelium [31]. Monocytes follow a chemoattractant gradient and migrate into the sub-endothelial space, become tissular macrophages, capture oxidized low-density lipoprotein cholesterol (LDL) and develop into foam cells. Apoptosis of the latter favor the accumulation of lipids in the sub-endothelial space forming the atheromatous plaques, which become coated by a fibrous shelter and promote platelet adhesion. Apoptosis of endothelial cell exposes the fibrous cap which in association with the enzymatic destruction of the extracellular matrix induce plaque rupture, exposure of pro-thrombotic plaque components, and subsequent thrombus formation that leads to vascular occlusion and CVD related events (myocardial infarction or stroke) [3].

Periodontitis patients have increased platelet recruitment and platelet hyperactivation as sustained by the augmented plasma concentration of platelet factor 4 (PF4) [32, 33]. Moreover, periodontitis has been frequently accompanied by a prothrombotic state. In patients with mild, moderate, or severe periodontitis D-dimer values were found to be increased by 1.62-fold, 2.06-fold and 2.54-fold, respectively than in healthy patients [34].

3. Epidemiologic relationships between periodontitis and CVD

Although, the relationship between periodontitis and CVD has long been the subject of debate in the scientific literature, the existence of a moderate association between periodontitis and CVD was firstly reported by a systematic review in 2003 [35]. Since then, many other systematic reviews and meta-analyses highlighted this idea. Periodontitis patients had 19%, 15% and 14% increased risk of developing CVD, respectively [36–38].

Individuals with active periodontitis had a nearly 2–2.5-fold higher risk of developing acute myocardial infarction than those without the disease [39, 40].

A positive association between both severe and moderate periodontitis and acute myocardial infarction exists, which suggests a relationship between periodontitis severity and CVD [41].

A significant association was found between calcified carotid artery atheroma and the presence of periodontitis both in acute myocardial infarction (OR, 1.51; 95% CI, 1.09–2.10) and controls (OR, 1.70; 95% CI, 1.22–2.38) [42]. Periodontitis was associated with a 45% higher risk of acute myocardial infarction (OR, 1.45; 95% CI, 1.10–1.91), whilst patients with both periodontitis and calcified carotid artery atheromas had a 75% higher risk for acute myocardial infarction then those without these conditions [42].

An increased CVD burden in patients with significant periodontal destruction had been suggested in different studies. Data from the Oral Infections and Vascular Disease Epidemiology (INVEST) study showed that the number of missing teeth was significantly associated with carotid artery plaque after adjustment for CVD risk factors [43]. Moreover, the Periodontitis and Its Relation to Coronary Artery Disease (PAROKRANK) study reported an increased risk of myocardial infarction in patients with periodontitis (odds ratio of 1.28, 95% confidence interval (CI) 1.03–1.6) after adjustment for some behavioral, social and medical risk factors. The radiographic

bone loss was used to quantify periodontal destruction [44]. However, concerns have been raised in relation to the difficulty to control for all possible confounders and the possibility that periodontitis could still be a surrogate for other risk factors not highlighted by these studies [45].

Periodontitis may also represent a risk factor for stroke, especially in ischemic events. However, new studies with a robust design are necessary for a reliable conclusion [46].

4. Periodontitis and hypertension

4.1 Epidemiological associations between periodontitis and hypertension

Hypertension is considered a major risk factor of CVD. Periodontitis has emerged as a new contributor to the complete cardiovascular risk profile of CVD.

The associative relationships between periodontitis and hypertension are important in the context of the high prevalence rates of both diseases that induce important medical and social burden. Besides the fact that periodontitis and hypertension share a group of common risk factors (older age, smoking, low socioeconomic and education status, genetics) an independent association between the two diseases has been reported.

The data provided by prospective and retrospective studies reported a higher prevalence of hypertension in patients with periodontal disease ranging from 7 to 77% as compared with patients without periodontitis with prevalence rates ranging from 4 to 70% [47]. Periodontitis patients had 4.5 mmHg higher systolic and 2.0 mmHg higher diastolic blood pressure than non-periodontitis patients [47]; the systolic component of the blood pressure seemed to be more influenced by periodontitis than the diastolic one [48].

Two meta-analyses provided information sustaining the association between periodontitis and hypertension [47, 49]. The heterogeneity of case definitions of both hypertension and periodontitis prevented the drawing of firm conclusions regarding this topic. The association between the two diseases is open to future analyses of data provided by clinical trials using uniform case definitions for periodontitis and hypertension.

The activity of periodontitis monitored through local inflammation index (bleeding on probing) seems also to play an important role in the complex interplay between periodontal disease and hypertension. Data from the Third US National Health and Nutrition Examination Survey (NHANES III) informed that local gingival inflammation (bleeding on probing) was significantly associated with increased systolic blood pressure (2.6 mmHg higher values compared with noninflamed situations) and increased risk of uncontrolled blood pressure after multivariate adjustments of a large make-up of influencing factors including systemic inflammatory diseases as well as behavioral and social factors [50]. Moreover, data from observational studies reported that even for patients on intensive antihypertensive treatment periodontitis was associated with an increased risk of uncontrolled hypertension [48].

The genetic background has been involved in the development of both periodontitis and hypertension at least partially by the modulation of immune-inflammatory reactions that sustain a proinflammatory milieu [48].

The high-salt diet is a common trigger for hypertension, but data has also shown to alter the microbiome and impair immune systems through salt-induced hypergluco-corticoidism [51, 52].

4.2 Periodontitis and pregnancy hypertensive disorders

It was proven that oral health among vulnerable populations, such as pregnant women is an important determinant regarding the pregnancy outcome. Numerous epidemiological studies have demonstrated an increased risk of adverse pregnancy outcome (APO), including preterm birth, low birthweight and pregnancy-induced hypertension or pre-eclampsia (PE) as well as gestational diabetes (GDM), related to periodontal disease [53]. Therefore, maintaining optimal maternal oral hygiene is regarded as a mandatory standard of care for perinatal medicine [54].

The reported prevalence of periodontitis, during the time period of pregnancy, varies between 10 and 74% and it is highly dependent on the economical level and health policies of each country [55].

Two pathogenic mechanisms described the potential effect of periodontal diseases on pregnancy outcomes. On the one hand, the periodontal bacteria could induce bacteremia and a seeding of the feto-placental unit. On the other hand, inflammatory mediators such as interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor-α (TNF-α) or prostaglandin E2 (PGE2), secreted by the subgingival inflammatory site are carried to the feto-placental unit, where an inflammatory response will develop [53].

The influence of the gingival bacterial microbiome on APO is confirmed by the new data that revealed the presence of a unique bacterial load even of the placentar tissue. Gram-positive as well as Gram-negative intracellular bacteria were identified in the basal plate of the human placenta [56]. Moreover, due to metagenomic technology, it was shown that placental microbiome profiles are more related to the oral microbiome than other microbiomes in the human body, such as the gut, nares, skin and urogenital tract [57].

The feto-maternal unit is exposed to oral bacteria during bacteriemia episodes caused by daily oral activities (e.g., tooth brushing and flossing) and dental treatments (e.g., scaling and root planing). Katz et al. identified the presence of *Porphyromas gingivalis* antigens in placental tissues and suggested that the colonization of *Porphyromas gingivalis* in the placenta might contribute to the placental dysfunction, a specific obstetrical feature in severe cases of PE [58]. Moreover, the presence of *Porphyromas gingivalis* in the umbilical cord was highly associated with PE. Several meta-analyses found a risk at least twice higher to develop preeclampsia in women diagnosed with periodontitis [59, 60].

The relationship between hypertensive disorders (including both pregnancy preexisting hypertension and pregnancy-induced hypertension, also called preeclampsia) and periodontitis was mostly explained in relation to the systemic inflammatory response due to maternal infection. In severe cases of periodontitis, the inflammatory mediators (alarmins) and cytokines found in the gingival mucosa, including IL-1β, IL-6, TNF-α and PGE2, entered systemic circulation and affect the feto-placental unit and myometrium [53].

The adequate invasion of the extravillous trophoblast in the vascular layer of spiral uterine arteries will determine appropriate feto-maternal perfusion. In vitro models showed the local interaction between the placental tissue (human trophoblast cell lines) and periodontal pathogens, bacterial components, or inflammatory mediators. According to the data, the inflammatory milieu may suppress the media layer invasion process, leading to an important vascular remodeling. Eventually, that will trigger the development of pregnancy-induced hypertension or will aggravate the chronic vascular changes in pregnant women with preexisting hypertension. This will further cause placental insufficiency, the physiopathological final step to the development of fetal distress in utero [61].

5. Periodontal therapy and cardiovascular risk

Non-surgical treatment of periodontitis refers to subgingival instrumentation of periodontally affected teeth and addresses the polymicrobial aetiologic factor from the subgingival areas. Full-mouth subgingival instrumentation performed within 24 hours has been proposed to prevent the dissemination of bacteria from non-instrumented pockets to the previously treated areas [62]. It is also worth mentioning that in severe generalized periodontitis, due to the mobilization of a huge mass of bacteria from the periodontal pockets, the full-mouth instrumentation could trigger an acute systemic inflammatory response associated with transient endothelial dysfunction [63]. Delivering subgingival instrumentation conventionally in several short sessions could overcome the systemic response and the theoretical short-term risk of developing a vascular event [64].

Data from observational studies observed no effect or just a minimal elevated risk of "*invasive dental treatment*" [65, 66] in augmenting the ischaemic cardiovascular risk. The report concluding that the "*invasive dental treatment*" had no effect in increasing the risk of myocardial infarction was based on the *Taiwanese National Health Insurance Research Database* and included more than 110,000 myocardial infarction patients and 290,000 ischaemic stroke patients over a period of 14 years. However, a modest risk of myocardial infarction during the first week after treatments has been indicated (OR = 1.31, 95% CI [1.08; 1.58], after 3 days). A self-controlled case series on about 10 million persons from an US insurance database reported that "*invasive*" dental treatments, mostly represented by tooth extractions, were associated with an augmented risk of incident acute cardiovascular events (IR = 1.5, 95% CI [1.09; 2.06]) within 1 month after therapy [66]. A small-scale clinical trial reported no cardiovascular adverse events within 3 months after periodontal subgingival instrumentation in patients with established CVD [67]. Also, a randomized secondary prevention trial showed that subgingival instrumentation in patients with established CVD was not associated with an increased incidence of cardiovascular events in 6 months after periodontitis treatment [68]. Moreover, a study on 5297 subjects, with a median follow-up period of 16.8 years concluded that individuals who did not respond well to periodontal treatment had a 28% increased risk for future CVD, indicating that successful periodontal treatment might influence the progression of subclinical CVD [69].

However, nowadays conclusions on this topic sustain that no association between "*invasive*" periodontal treatments and an increased incidence of myocardial infarction or ischaemic cardiovascular risk has been reported [8, 70].

6. Perioperative bleeding risk associated periodontal procedures

6.1 Bleeding risk of periodontal procedures

The perioperative bleeding risk depends on the extent and invasiveness of the periodontal therapeutic approach. A low bleeding risk has been mentioned for most periodontal interventions such as subgingival instrumentation, conventional surgeries (debridement flaps and regenerative or resective interventions), dental implants placement, or tooth extraction [8]. The bleeding associated with these interventions

could be controlled through local haemostatic measures. On the other hand, a moderate bleeding risk is considered for autogenous bone augmentation procedures including block bone harvesting and sinus floor elevation or interventions associated with secondary intention healing such as free gingival graft placement [71, 72]. The frequencies for low and moderate bleeding associated with periodontal therapies have been reported to be less than 1% and between 2 and 5%, respectively [8].

6.2 Patients undergoing antiplatelet and anticoagulant therapy

Single antiplatelet therapy such as acetylsalicylic acid (aspirin), clopidogrel, ticlopidine or ticagrelor did not increased the frequency of bleeding events as compared with control patients [73, 74].

Dual antiplatelet therapy usually using the combination of aspirin and clopidogrel may induce a certain risk for post-operative bleeding, which may be managed with local haemostatic approaches [75, 76].

The discontinuation of single or dual antiplatelet therapy before any kind of periodontal approach including dental implant placement is not recommended by current evidence [8].

"Current American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, European Society of Cardiology, American College of Chest Physicians Evidence-Based Clinical Practice (AHA/ACC/SCAI/ACS/ADA/ESC/ACCP) guidelines on perioperative management of antithrombotic therapy do not suggest discontinuation of anti-platelet therapy for low bleeding risk procedures" [77–79].

No increased risk of bleeding has been associated with oral vitamin K antagonist-anticoagulant therapy (warfarine, cumarine) in patients receiving dental extraction, minor dental procedures or dental implant placement when compared to patients discontinuing anticoagulant therapy [80, 81]. However, in comparison with non-vitamin K patients, a higher post-operative bleeding risk in patients continuing vitamin K antagonist-anticoagulant therapy and suffering from minor or higher-risk dental procedures have been reported, although post-operative bleeding could be effectively controlled with local haemostatic agents [80, 82, 83].

As for novel/direct anticoagulants such as apixaban, rivaroxaban, betrixaban, edoxaban, and dabigatran, it seems that the interruption of these drugs is not necessary for most dental-periodontal therapies, due to a low incidence of bleeding events associated with these drugs and which can be successfully managed with local haemostatic measures [84–86]. As a positive advancement in the field, a neutralizing agent (idarucizumab) has been developed for dabigatran. However, a higher incidence of delayed bleeding (2 days and later) has been reported in patients not discontinuing novel/direct anticoagulants in comparison with healthy persons [87]. Although, it has been widely used in the past, especially in the era of anti-vitamin K anticoagulants, the low molecular weight heparins (LMWH) bridging strategy should be avoided in patients treated with novel oral anticoagulants (NOAC) as it increases the risk of bleeding, with no benefit on the risk of cardioembolic events. It is reserved for patients with mechanical valve prostheses at high thrombotic risk [88].

However, in CVD patients receiving complex antithrombotic medication a strict communication with cardiologist is mandatory.

7. Periodontitis and CVD: recommendations for clinicians and patients

7.1 Recommendations for periodontologists treating patients with CVD

a. Patients with medium or severe generalized periodontitis without known CVD should [8]:

- be advised that periodontitis induces a higher risk of CVD and its acute events (myocardial infarction and stroke)
- actively manage all their CV risk factors such as smoking, lack of exercise, excess weight and blood pressure, lipid, and glucose profile
- receive intensive periodontal therapy and tailored oral hygiene education and regimen
- receive a strict scheduled periodontal maintenance
- be referred to the cardiologist for CVD screening if CVD risk factors are present.

b. Patients with periodontitis and CVD should:

- be informed that they may be at higher risk for CVD complications
- receive active periodontal treatment and tailored oral hygiene education and regimen
- be included in periodontitis regular maintenance and secondary preventive regimes.

c. People with CVD should:

- be referred by the cardiologist to the periodontist for a thorough full-mouth oral examination and screening
- receive a tailored oral hygiene education and regimen
- be placed on a preventive care regime if no periodontitis is diagnosed and monitored regularly (at least once a year) for changes in periodontal status
- be managed as for point b) if periodontitis is diagnosed.

d. Subgingival instrumentation in periodontitis patients with CVD should be provided preferably in several 30- to 45-minute sessions to reduce the putative acute systemic inflammation.

e. In patients with CVD, surgical periodontal and implant therapy when indicated should be provided similarly as in patients without CVD.

f. In hypertensive patients, high blood pressure above 180/100 indicates to postpone periodontal surgical procedures until stabilization of blood pressure.

g. In patients with antiplatelet and anticoagulant therapy

- The periodontist should not modify the patient's antiplatelet and anticoagulant medication to perform periodontal and implant surgeries which are associated with a low to medium risk of bleeding.
- A consultation with the cardiologist is advised when doubts are raised.
- Local management of bleeding complications should be considered such as: oxidized cellulose, absorbable gelatine sponges, sutures, tranexamic acid mouthwashes, compressive gauze soaked in tranexamic acid.
- It has been suggested to discontinue vitamin K antagonist-antithrombotic therapy if the Internationalized Normalized Ratio (INR) ≤ 4 for low or medium bleeding risk surgeries, but the decision should be considered in consensus with the cardiologist. For INR ≥ 3.5 the advice of the responsible specialist is mandatory [8, 89].
- For non-vitamin K novel and direct anticoagulant (NOAC/DOAC) and when low bleeding risk periodontal approaches are scheduled, the anticoagulant therapy should not be discontinued [8, 71, 72]. Periodontal procedures should be undertaken within 18–24 hours after the last intake (depending on a renal function assessment for the medication in question) after which medication intake should be resumed after 6 hours following treatment.
- **For all intentions to adjust antithrombotic therapy to perform periodontal surgeries the periodontologist should consult with the responsible cardiologist.**
- **If discontinuation of antithrombotic therapy is planned for medium bleeding risk periodontal approaches, the decision should be made in agreement with the cardiologist**.
- In higher thrombotic and ischaemic risk patients (i.e., chronic atrial fibrillation or after an acute myocardial infarction or recent coronary stenting) receiving combined antiplatelet and anticoagulant therapies, **all periodontal treatments and antithrombotic change intensions (either of low or medium bleeding risk) must be discussed and agreed upon with the responsible cardiologist** [8, 71, 72]. The periodontal interventions should be eventually delayed.
- Patients under **triple therapy** (dual antiplatelet and one anticoagulant) or one **anticoagulant plus one antiplatelet should be individually managed** in consensus with the responsible cardiologist and eventually referred in dental specialized care centres [79, 90].

h. Patients with a risk of endocarditis should be premedicated with antibiotics following current guidelines (such as the European or the American guidelines).

i. People with CVD who have extensive tooth loss should be encouraged to pursue dental rehabilitation to restore adequate mastication for proper nutrition.

j. Diet counseling including low salt consumption could be beneficial for the management of both periodontitis and hypertension.

k. CVD including hypertension could benefit from periodontitis primary and secondary prevention.

7.2 Periodontitis-related recommendations for physicians and cardiologists

a. Cardiologists should know that periodontitis is a highly prevalent disease that has potentially negative influences on CVD development and complications as well as that efficient periodontal treatment may positively impact CV status.

b. **Cardiologists should advise all CVD patients on the above-mentioned topic and to seek periodontal specialized care as part of their ongoing management of CVD.** Even if no periodontitis is diagnosed initially, an annual oral check-up is recommended.

c. For patients already diagnosed with periodontitis, the cardiologist must ensure that the disease has been effectively treated.

d. The cardiologist should assist the periodontist in the management of patients under antithrombotic therapy before the periodontal surgery, to avoid risks of bleeding or ischaemic events.

7.3 Recommendations for patients with CVD or at risk of CVD in relation with periodontitis

a. Patients with CVD should know that:

- periodontitis is a chronic infectious disease having the potential to worsen their systemic condition
- periodontitis is treatable in most cases but requires lifelong personal management and professional supervision
- left untreated periodontitis leads to further bone destruction and finally to tooth loss
- periodontitis is a "silent" disease so regular dental-periodontal check-ups are advised
- periodontitis treatment has a positive impact on CVD and reduces the risk of CV events
- **they need to seek periodontal specialized screening for periodontitis and eventually care as part of their ongoing management of CVD**
- an annual oral check-up is recommended even in the absence of periodontitis.

b. Periodontitis patients are important co-therapists and without their sustained daily involvement, periodontitis resolution is not possible.

c. Patients with CVD and periodontitis, like all the other individuals, must efficiently clean the teeth based on the dental practitioner/periodontist personalized advice. The following oral care recommendations should be practiced:

- Tooth brushing twice a day with an electric or a manual toothbrush is recommended; however, electric toothbrushes seem to be more efficient than manual toothbrushes in a personalized local hygiene routine.

- Cleaning the areas between teeth using auxiliary oral hygiene aids is mandatory since using only conventional toothbrushing is not sufficient for complete plaque removal. Interdental brushes, carefully calibrated to fit the size of the interdental spaces should be used. Dental floss is an interdental cleaning option that can be used whenever the gums fill in the interdental spaces.

8. Conclusions

Periodontitis has been considered a risk factor for CVD, although no causal relationship has been demonstrated to this point. Two potential biological mechanisms (periodontal bacteria and endotoxins systemic dissemination and release of inflammatory molecules from the affected periodontal sites into the blood stream) have been described to link periodontitis and atherosclerosis-induced CVD. Periodontitis may increase the risk for hypertension as well as for acute CV events—myocardial infarction and stroke. In pregnant women, periodontitis may trigger adverse pregnancy outcomes and may worsen the chronic vascular changes in relation with pre-existing hypertension, which carries high maternal and fetal health risks. Periodontal screening in specialized medical care settings should be a component of the management of CVD. Periodontologists, cardiologists, and patients should be informed on the potentially negative influences of periodontitis on CVD development and its complications as well as on the positive impact of periodontitis treatment on CV status. All adjustments in antithrombotic treatment in periodontitis-CVD patients must be discussed and agreed upon with the responsible cardiologist.

Conflict of interest

The authors declare no conflict of interest.

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