Periodontitis as A Risk Factor of Unprovoked Venous Thromboembolic Disease: An Emerging Association

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ABSTRACT
Venous thromboembolism is a multifactorial disease. Major provoking factors are identified in 50–60 % of patients, but 40-50% of cases remain unexplained. In recent years, the role of chronic inflammatory disorders has been extensively investigated. Recently, immunothrombosis could explain some cases of “unprovoked” VTE. The inflammation may have an influence on three key elements of coagulation: initiation and propagation of coagulative cascade; downregulation of natural anticoagulants; inhibition of fibrinolytic pathway. Several components of the immune system, including cytokines, different types of leukocytes and platelets are involved in underlying inflammatory processes of VTE. In recent years, periodontal disease has been related to a large number of systemic disorders and relationship is observed between the presence of periodontitis and venous thromboembolic disease. Porphyromonas gingivalis, a Gram-negative anaerobic bacterium, is the major etiologic agent which contributes to chronic periodontitis. Periodontopathogenic bacteria are able to provoke endothelial dysfunction, platelets activation, inflammatory cytokines production, and autoimmune reactions that lead to thrombin generation. The periodontitis could therefore explain a non-negligible percentage of unprovoked venous thromboembolic disease.

Keywords: immunothrombosis, inflammation, vascular disease

1. INTRODUCTION
Venous thromboembolic disease (VTED) is a major public health problem around the world, for high prevalence (1/1000 persons/years) [1], high recurrence, morbidity, mortality and health cost [2]. Veins of the lower limbs are more often interested (deep venous thrombosis - DVT) [3], but it can also be localized in unusual sites. In 30% of cases it can be complicated by pulmonary embolism (PE) that is held responsible until to 5-10% of hospital deaths [4]. In 50-60 % of cases, VTED is secondary to know risk factors, whose presence explains its onset and the risk of

recurrence, whose elimination plays an important role in the prophylaxis and treatment [5]. However, in 40-50% of patients, venous thromboembolic (VTE) events remains unexplained and requires lifetime anticoagulant treatment [6]. Minor risk factors can explain unprovoked VTED and have been highlighted in recent years. For many other minor risk factors, inflammation appears to be the most likely common link [7]. In the last few years a lot has been clarified on the relationship inflammation and coagulation: inflammation leads to the activation of coagulation (more inflammation, more thrombin is generated) and coagulation in turn produce inflammation. In general, infection disease represents a risk factor of VTE events [8]. Periodontitis is a chronic inflammatory disorder of the supporting dental structures characterized by weakening of the periodontal ligament, alveolar bone reabsorption and often loss of the tooth. In recent years periodontitis has been associated with systemic disorders and it’s considered a risk factor for atherosclerosis [9], cardiovascular [10] and kidney disease development [11]. Association with VTED is not clear yet despite being less analyzed. Some hypotheses have been formulated, such as the association with endothelial dysfunction and valve insufficiency in varices.

2. METHODS

We analyzed the recent years literature on the periodontitis and VTED association. Bibliographic research was conducted on EMBASE and PUB MED inserting the keywords « periodontitis and venous thromboembolism » or « inflammation and venous thromboembolism ». Inclusion criteria were: only articles in English; in vivo and in vitro studies; original articles or case series; reference to period 1990-2018. Exclusion criteria were: articles in other languages than English; other that in vivo and in vitro studies; case reports; articles prior to 1990.

3. RESULTS

For the first time presence of periodontopathogenic bacteria (Porphyromonas gingivalis and Treponema denticola) in saphenous vein specimen was reported in 2007 and its role as a potential risk factor for the development of varices was highlighted [12]. Sánchez-Siles et al. in a cross-sectional case-control study found a periodontitis prevalence of 73.19% in VTED patients and 45.00% in control group with particularly higher frequency of severe forms in the VTED-group [13]. The same authors in another report found higher Dimer D levels in a periodontitis-group that in control group, iphotesizing a role of unprovoked VTED independent risk factor for periodontitis [14]. The Atherosclerosis Risk in Communities Study (ARIC), a multi-site prospective cohort study conducted in four U.S. communities showed association of periodontitis and risk of VTED in patients with tooth loss (adjusted HR 1.42) and edentulous patients (adjusted HR 1.51) [15].

4. DISCUSSION

Periodontitis is a chronic inflammatory disease of the gum and bone support surrounding the teeth characterized by formation of pockets or spaces between tooth and gums, and alveolar bone loss. Periodontitis is classified into four stages according to severity and complexity of management (table 1).

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Initial periodontitis</th>
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<tr>
<td>Stage II</td>
<td>Moderate periodontitis</td>
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<tr>
<td>Stage III</td>
<td>Severe periodontitis with potential for additional tooth loss</td>
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<tr>
<td>Stage IV</td>
<td>Severe periodontitis with potential for loss of dentition</td>
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Severity : Interdental clinical attachment level (CAL) at site with greatest loss; Radiography bone loss and tooth loss.

Complexity of management: Probing depths, pattern of bone loss, furcation lesions, number of remaining teeth, tooth mobility, ridge defects, masticatory disfunction.

Thrombosis is a pathological process due to the participation of coagulative cascade and several blood cells. When this process is aimed at the elimination of pathogens, it becomes a defense mechanism recently redefined immunothrombosis [16]. Immune cells and several molecules produce a defensive scaffold which facilitates recognition, containment and elimination of pathogens. Interaction between bacteria and immune...
cells involves specific receptors. This pattern recognition receptors (PPR) in immune cells are active to link specific molecular pattern of microbes (PAMPs) and damage associated molecular pattern (DAMPs). Endothelial dysfunction is a link between infection and venous thrombosis. Normal endothelium has antithrombotic and fibrinolytic properties. Endothelial dysfunction causes vasoconstriction via endothelin production and nitric oxide (NO) inhibition, vasal remodeling via growth factors production, inflammation via cytokines production and expression, and hypo-fibrinolysis via PAI-1 production [17]. Chronic inflammation leads to permanent activation of the hemostatic balance through up regulation of activation and downregulation of the coagulation inhibitors, such as C protein pathway [18]. Bacterial lipopolysaccharide (LPS) play an important role in endothelial cells (EC) activation through stimulation of monocytes to produce interleukin-1 (IL-1), tumor necrosis alpha (TNF-α) and transforming growth factor beta (TGF-β) and interleukin 6 (IL-6) hepatic production. IL-6 levels correlate with higher fibrinogen and CRP, costing a marker of lower survival, recurrence rate and complications following DVT also post-thrombotic syndrome [19]. Porphymonas Gingivalis (PG) is one of the most important pathogens in periodontitis development. There are many factors that influence its pathogenicity, such as release of proteases named « gingipains » [20], PG, as well as Eikenella Corrodens and Prevotella Intermedia, other periodontopathogenic bacteria, have to ability to directly invade EC with expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1), P-selectin, E-selectin and toll like receptor 4 (TLR4) and secretion of tissue factor (TF). Furthermore, TF is released by monocytes cells activated from bacterial LPS and inflammatory cytokines. This is followed by recall of leukocytes and platelets. Conversely, platelets are directly activated by gingipains of PG via protease-activated receptors (PAR-1 and PAR-4) [21]. cPLT interacts with various bacteria such as P. gingivalis [22]. They adhere and aggregate around bacteria via glicoprotein Ibα (GP1bα) that bind von Willebrand factor (vWF). However, in small venules, where there is a higher shear stress, an interaction between endothelial P-selectin and platelet P-selectin glycoprotein ligand 1 (PSGL1) occurs. Additional signal is necessary between endothelial ICAM-1 and platelet GP2b/3a in a fibrinogen-dependent manner. We know that activated EC express E/P selectins, ICAM-1 and VCAM. EC activation can be mediated by the same cPLT through CD40ligand (CD154) surface expression and IL-1β secretion under inflammatory stimulus. Conversely, cPLT form aggregates with leucocytes through link of P-selectin to PSGL1 and CD40 to CD40L, respectively, but also through toll-like receptors (TLR) 2, 4 and 7. TLRs can initiate the thrombotic process. Platelet morphology in the PLT-leucocytes aggregates is typical: smaller PLT with fewer pseudopodia connecting to other PLT and leucocytes. In infection, platelets interact with neutrophils forming the neutrophil extracellular traps (NETs), a network of extracellular fibers formed by stretches of DNA, histones and enzymes (myeloperoxidase, gelatinase, elastase and cathepsin G) [23]. The most power activator inducing NETs is bacterial LPS via TLR4. NETs capture in the microvasculature, prevents dissemination and concentrates pathogens, and recruits other immune cells for bacteria killing. NETs caused platelet adhesion, activation and aggregation and histones are essential in this regard. Serine proteases inhibits tissue factor pathway inhibitor (TFPI), amplifying TF liberation. Dysregulation of NETosis and its relationship to thrombosis has been recognized in various clinical settings such as venous VTED. After a venous thromboembolic event circulating NETs increased 48 h later and persisting through 6 days. Myeloperoxidase (MPO) reaches its peak 24 h after, slowly decreases and returns to its basal level within seven days. MPO, extracellular DNA, nucleosomes and α-1 antitrypsin elastase (as a neutrophil activation markers) are significantly elevated, correlates with D-dimer levels and they can therefore represents potential diagnostic targets [24]. NETs also lead to autophagy-induced release of TF, and NETs further stimulate FXII activation, starting both intrinsic and extrinsic coagulation cascades and thrombin formation and finally to the conversion fibrinogen to fibrin [25]. Finally, the heat shock protein 60 (HSP60) of PG (GroEL) is very similar to human endothelial HSP60 [26] and this can lead to autoimmune cross reactions and T reactive lymphocytes activation. Furthermore, it lead

macrophages TLR2 and TLR4 activation. Inflammatory response leads lower expression of endothelial Oxido Nitrico Synthase (NOS) resulting in reduced production of NO [27] and free radicals increase (figure 1).

Figure 1: Pathogenic mechanisms of venous thrombosis

5. CONCLUSION

Chronic infection is a risk factor of unprovoked venous thromboembolism through a well-established link between inflammation and coagulation. Preliminary study shows a relationship between periodontitis and VTED. Future research and prospective studies are needed to confirm the association between these two diseases. Disease prevention and oral health promotion are essential to encourage people to implement healthy lifestyles rather than to treat teeth. In addition, the connection between oral health, general health and health-related quality of life will necessitate a multidisciplinary approach to prevention and oral health promotion. Dietary advice to prevent dental caries and smoking cessation counseling to prevent periodontal disease and oral cancer also promote general health. Consequently, physician, dentists and dental hygienists are very important persons in the dental team of the future.
REFERENCES