

ORIGINAL ARTICLE

Periodontal disease as a risk factor of recurrence of venous thromboembolic disease: a prospective study

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Abstract

Background. In recent years, periodontal disease has been related to a large number of systemic disorders. **Objective.** To study the possible relationship between periodontal disease and high levels of D-dimer in a group of patients with venous thromboembolic disease. **Materials and methods.** A study was made of 142 patients diagnosed with unprovoked venous thromboembolic disease. All patients underwent oral examination consecutively and randomly. Finally, two groups were obtained: (a) patients with periodontal disease ($n = 71$); and (b) patients without periodontal disease ($n = 71$). All patients were subjected to periodontal study, with evaluation of the number of teeth, bleeding index, gingival index, simplified oral hygiene index, community periodontal index of treatment needs, clinical attachment level, probe depth, number of pockets ≥ 4 mm, number of pockets ≥ 6 mm. The D-dimer values were evaluated in both groups. **Results.** D-dimer values were higher in the study group than the control group, with statistically significant differences ($p = 0.010$). **Conclusions.** A relationship is observed between the presence of periodontal disease and high D-dimer levels. Patients with venous thromboembolic disease and periodontal disease could have more risk of a new thromboembolism episode.

Key Words: periodontal disease, venous thromboembolic disease, D-dimer

Introduction

Venous thromboembolic disease (VTED) is a common disorder with an annual incidence of about one case per 1000 person-years [1]. In one-third of the patients, deep venous thrombosis (DVT) is complicated by embolization of the clot into the pulmonary artery.

The short-term mortality associated with pulmonary embolism (PE) is high and mainly depends on the age of the patient and the presence of underlying comorbidities such as cancer or cardiorespiratory disease [1,2]. VTED is a chronic disease that often recurs. In non-selected cohorts of patients with venous thrombosis, the risk of recurrence after 5 years is 20–25% and exceeds 25% in patients with unprovoked venous thrombosis. The recurrence risk is mainly dependent on the presence or absence of acquired and congenital risk factors and can vary substantially between patients [3]. Many clinical

and laboratory risk factors for recurrent venous thrombosis have been established. Nevertheless, the prediction of recurrence in a given patient remains a challenge [4]. The natural course of VTED is still poorly understood and many risk factors of the disease are yet to be discovered [4].

The risk of thrombosis is especially high in patients in which the initial thrombotic event was unprovoked (i.e. without antecedents of surgery, trauma, pregnancy or female hormone treatments). Some clinical features are associated with a high risk of recurrent thrombosis, such as the absence of a temporary risk condition [5], PE or proximal deep vein thrombosis [3,6], the occurrence of more than two thrombotic events [3,7], the male sex [8], cancer [9], post-thrombotic syndrome [10], excess body weight [11], residual vein thrombosis [12], hormone treatment, surgery of the lower extremities, pregnancy and congenital and acquired thrombophilia, among others [4].

D-dimer is a cross-linked fibrin blood clot degradation product and its levels are typically elevated in patients with acute venous thromboembolism. D-dimer assays are generally sensitive but non-specific as markers of VTED and, because of the high negative predictive value (NPV) of D-dimer, measurement of the concentration of D-dimer has become an integral part of many diagnostic algorithms to exclude acute DVT and PE [13]. The measurement of D-dimer concentrations can be used to separate patients into groups at high or low risk of recurrent venous thrombosis. Patients with an especially low risk of recurrence can be identified with lower cut-off concentrations for D-dimer. Patients with a first episode of unprovoked DVT or PE and D-dimer concentrations of <250 ng/ml have a 60% lower recurrence rate than those with concentrations ≥ 250 ng/ml [14].

Periodontal disease (PD) is an inflammatory disorder of the tooth-supporting structures that leads to the destruction of connective tissue, loss of periodontal attachment and resorption of alveolar bone [15].

In recent years, many studies have attempted to establish a relationship between periodontal disease and certain systemic disorders [16] such as diabetes [17], pulmonary disease [16], kidney disorders [18], cardiovascular disease [19], endometriosis [20] and other diseases [21]. Some studies have considered PD as a risk factor for vascular endothelial damage [22,23] and valve incompetence in varicose veins [24] also being both risk factors for VTED. In this sense, a high frequency of PD was detected in a group of patients suffering from VTED in the Thromboembolic Unit of the University Virgen de la Arrixaca Hospital.

The present study evaluates the possible correlations of periodontal disorders and high D-dimer levels, regarded as an indicator of thromboembolic recurrence risk in a group of patients with VTED.

Materials and methods

A cross-sectional case-control study involving 142 patients was carried out. The inclusion criteria were age over 18 years, a confirmed diagnosis by objective methods (doppler ultrasound for DVT and computed tomographic angiography for PE) of unprovoked VTED and the obtainment of written informed consent. The exclusion criteria were totally edentulous individuals and the presence of ≤ 5 teeth, diabetes mellitus, pregnancy and breastfeeding, presence of risk factors of VTED, anticoagulation treatment at the moment of the study and failure to sign the informed consent document.

Once diagnosed as VTED, all patients began treatment with heparin and in a few days, which can be variable, all started with Sintrom[®] (acenocumarol) (Novartis Farma S.p.A, Origgio, Italy) treatment.

Anticoagulation was maintained for a minimum of 3 months, then, if the D-dimer values, ultrasound and computed tomographic angiography were normal, anticoagulation was removed for 1 month. After this month all patients were reviewed and the D-dimer test was requested again in order to resume or not anticoagulation treatment. At this time we carried out the periodontal evaluation of all subjects.

A total of 13 subjects were excluded (five pregnant women, three breastfeeding women and five totally edentulous individuals). The final study group, therefore, comprised 142 patients: 63 men and 79 women, with a mean age of 60.54 ± 14.01 years (range = 21–91 years). Of these subjects, 71 suffered periodontal disease, while 71 were healthy controls. Both groups were homogeneous in terms of age and sex ($p = 0.121$ and $p = 0.866$, respectively). The study was carried out in the Thromboembolic Disease Unit of Virgen de la Arrixaca University Hospital (Murcia, Spain) between January 2009 and March 2012, following approval from the Ethics Committee of the University of Murcia. A data collection protocol was designed for registering demographic data such as age, sex and country of origin. From the patient medical records we documented the type of VTED (DVT or PE); body mass index (BMI); blood pressure; and blood laboratory test parameters, including complete blood count, biochemical parameters and coagulation (D-dimer Latex particle immunoassay, IL Test D-dimer). The cut-off point for D-dimer was ≥ 250 ng/ml [25].

Periodontal study in all the patients was carried out 4 months after diagnosis. Periodontal evaluation in turn was based on the number of remaining teeth and missing teeth, bleeding index [26], gingival index [27], simplified oral hygiene index (OHI-S) [28], community periodontal index of treatment needs (CPITN) [29], clinical attachment level (CAL) [30], probe depth (PD) [31], number of pockets ≥ 4 , number of pockets ≥ 6 and the classification of periodontal disease as either healthy, mild or severe [32]. The periodontal evaluations were made by the same dental surgeon. The diagnosis and follow-up of thromboembolic disease was carried out by the same specialist in internal medicine.

Statistical analysis

The data were analyzed using the SPSS version 12.0 statistical package (SPSS[®] Inc., Chicago, IL). A descriptive study was made of each variable. The associations between the different qualitative variables were studied using Pearson's chi-squared test. We, in turn, used the Student *t*-test for two independent samples in application to quantitative variables, in each case determining whether the variances were homogeneous. A bivariate analysis was also performed considering the binary parameter

Table I. Characteristics of the study population.

Characteristics of the sample	
Patients, <i>n</i>	142
Age, mean ± SD	60.54 ± 14.01
Sex, <i>n</i> (%)	
Male	63 (44.37)
Female	79 (55.63)
Obesity (body mass index ≥30 Kg/m ²), <i>n</i> (%)	59 (41.55)
Type of venous thromboembolism, <i>n</i> (%)	
Deep vein thrombosis	76 (53.52)
Pulmonary embolism	37 (26.05)
Deep vein thrombosis + Pulmonary embolism	29 (20.43)
Presence of high levels of D-Dimer, <i>n</i> (%)	
Normal D-Dimer level (<250 ng/mL)	58 (40.85)
Abnormal D-Dimer level (≥250 ng/mL)	84 (59.15)

SD, standard deviation.

‘presence of high levels of D-Dimer (≥250 ng/ml)’ as the outcome variable. Odds ratios and confidence intervals were calculated with exact conditional logistic regression. Statistical significance was accepted for $p \leq 0.05$.

Results

Of the 142 patients studied, 63 (44.37%) were men and 79 (55.63%) women. The mean age was 60.54 ± 14.01 years (range = 21–97). All the patients were diagnosed with VTED. Of these, 76 (53.52%) presented DVT, 37 (26.05%) suffered PE and 29 (20.43%) had both.

Table I shows some of the characteristics related to VTED in the global sample. Of the 142 subjects with

VTED, all of whom underwent oral examination consecutively and randomly, 71 patients had PD and 71 patients were periodontally healthy. Both groups were homogeneous in terms of the demographic characteristics, body mass index, blood pressure and type of VTED (Table II).

Dimer D levels in the periodontal group was 516.04 ± 498.21 and 324.13 ± 345.61 for the healthy control group ($p = 0.010$) (Table III).

Table IV shows an analysis of the different periodontal parameters and the presence of high D-dimer levels. We detected a lower bleeding index in patients with a higher level of D-dimer ($p = 0.045$).

A logistic regression model, developed (Table V) to determine whether certain variables (sociodemographic parameters, habits, periodontal disease, blood pressure) are related to the D-dimer levels, revealed statistically significant differences in the presence of periodontal disease ($p = 0.002$).

Discussion

The present study was designed to evaluate PD as a risk factor of venous thromboembolism recurrence in patients with VTED.

Selected patients for this study had no risk factors of VTED (unprovoked) and, at the moment of periodontal evaluation, none of them were under anticoagulation therapy, since anticoagulation reduces odds of D-dimer in most of the VTED patients.

The analysis of the possible relationship between periodontal disease and high D-dimer levels (regarded as a risk marker for thromboembolic episodes) showed statistically significant differences between periodontal disease patients and healthy periodontal patients. The risk of thrombosis is especially high in patients in which the initial thrombotic

Table II. Homogeneity of the study groups in terms of the demographic characteristics, body mass index, blood pressure and type of venous thromboembolism (Student *t*-test and Pearson χ^2).

Characteristics	Periodontal disease group (<i>n</i> = 71)	Healthy control group (<i>n</i> = 71)	<i>p</i> -value
Age, mean ± SD	62.37 ± 14.79	58.72 ± 13.02	0.121
Sex, <i>n</i> (%)			0.866
Male	32 (45.08)	31 (43.67)	
Female	39 (54.92)	40 (56.33)	
Body mass index (kg/m ²), mean ± SD	30.04 ± 5.46	29.03 ± 6.12	0.306
Systolic blood pressure, mean ± SD	130.34 ± 19.24	128.69 ± 19.62	0.614
Diastolic blood pressure, mean ± SD	76.80 ± 11.04	79.85 ± 10.32	0.094
Type of venous thromboembolism, <i>n</i> (%)			0.085
Deep vein thrombosis	44 (61.97)	32 (45.08)	
Pulmonary embolism	17 (23.94)	20 (28.16)	
Deep vein thrombosis + Pulmonary embolism	10 (14.09)	19 (26.76)	

SD, standard deviation.

Table III. Laboratory variables in the study groups (Student *t*-test).

Laboratory variables	Periodontal disease group (<i>n</i> = 71), <i>M</i> ± <i>SD</i>	Healthy control group (<i>n</i> = 71), <i>M</i> ± <i>SD</i>	<i>p</i> -value
Leucocytes (<i>n</i>)	7.45 ± 3.85	8.26 ± 2.55	0.157
Platelets (<i>n</i>)	248.35 ± 76.07	240.91 ± 77.13	0.576
D-Dimer (ng/mL)	516.04 ± 498.21	324.13 ± 345.61	0.010

SD, standard deviation.

Table IV. Relation between periodontal characteristics (only periodontal disease group) and presence of high levels of D-Dimer (Student *t*-test and Pearson χ^2).

Periodontal characteristics	Normal D-dimer level (<i><</i> 250 ng/mL) (<i>n</i> = 28)	Abnormal D-dimer level (<i>≥</i> 250 ng/mL) (<i>n</i> = 43)	<i>p</i> -value
Number of teeth, <i>M</i> ± <i>SD</i>	21.71 ± 7.31	17.70 ± 6.98	0.023
Bleeding index, <i>M</i> ± <i>SD</i>	67.89 ± 29.03	53.18 ± 30.16	0.045
Gingival index, <i>M</i> ± <i>SD</i>	2.00 ± 0.57	1.87 ± 0.76	0.477
OHI-S, <i>M</i> ± <i>SD</i>	1.60 ± 0.55	1.46 ± 0.65	0.370
CPTIN, <i>M</i> ± <i>SD</i>	2.33 ± 1.24	2.35 ± 1.08	0.956
CAL (mm), <i>M</i> ± <i>SD</i>	4.34 ± 0.91	4.61 ± 0.56	0.129
PD (mm), <i>M</i> ± <i>SD</i>	3.47 ± 0.92	3.51 ± 0.82	0.872
Number of pockets <i>≥</i> 4 mm, <i>M</i> ± <i>SD</i>	7.39 ± 6.32	6.91 ± 4.56	0.708
Number of pockets <i>≥</i> 6 mm, <i>M</i> ± <i>SD</i>	3.39 ± 5.58	2.98 ± 7.84	0.809
Periodontal disease, <i>n</i> (%)			0.294
Mild	13 (46.42)	25 (58.13)	
Moderate	6 (21.44)	11 (25.81)	
Severe	9 (32.14)	7 (16.06)	

SD, standard deviation; OHI-S, oral hygiene index-simplified; CAL, clinical attachment level; PD, probing depth.

event was unprovoked (i.e. without antecedents of surgery, trauma, pregnancy or female hormone treatments) [5]. The absence of risk factors make this type of VTED uncontrolled and unpredictable. There are some unknown VTED factors that can activate thromboembolic episodes. In this study we consider periodontal disease as a possible risk factor that could influence the recurrence of this acute, serious and frequently mortal disease.

Table V. Logistic regression model for 'presence of high levels of D-Dimer (*≥*250 ng/mL)'.^a

Variables	Odds ratio	95% CI	<i>p</i> -value
Age	0.61	0.31–1.26	0.185
Sex	1.72	0.88–3.37	0.111
Periodontal disease	0.33	0.16–0.65	0.002
Body mass index	0.98	0.44–2.16	0.968
Systolic blood pressure	1.05	0.54–2.04	0.867
Diastolic blood pressure	1.26	0.39–4.07	0.699
Leucocytes (<i>n</i>)	1.47	0.59–3.67	0.400
Platelets (<i>n</i>)	1.01	0.99–1.01	0.346

There is no precedent in the literature for this association. D-dimer is a biomarker that globally indicates the activation of hemostasis and fibrinolysis. Two hypotheses were proposed for explaining a possible potential relationship between the two disorders. In PD, during the colonization process of bacterial infection, the host immune system can cause tissue damage and in turn activate a humoral immune response [33]. Several autoimmune models have been suggested to explain the pathogenesis of periodontal disease. In this sense, the pathogenic roles of certain autoantibodies (anti-neutrophil cytoplasmic autoantibodies (ANCA), anti- β (1)-adrenergic antibodies) present in a number of autoimmune, inflammatory or vascular diseases have been cited in attempting to clarify common pathogenic mechanisms [34]. Inflammation associated to autoimmune disorders may be a risk factor for thromboembolism [35]. In this context, inflammation modulates the thrombotic response, up-regulating pro-coagulants, down-regulating anti-coagulants and suppressing fibrinolysis [36]. Inflammation and coagulation play a key role in the pathogenesis of vascular disease. There is growing evidence of extensive interference between

them: inflammation leads to the activation of coagulation and coagulation in turn considerably affects inflammatory activity [37].

On the other hand, a number of studies have pointed to certain anaerobic bacteria such as *Porphyromonas gingivalis*, implicated in PD, as risk factors for vascular endothelial damage [22,23]. Kurihara et al. [24] investigated the possible relationship between valve incompetence in varicose veins and chronic inflammatory PD, analyzing the presence of periodontopathogenic bacteria in the saphenous vein. The authors found 48% of the patients to prove positive for at least seven periodontopathogenic bacteria, including *Porphyromonas gingivalis* and *Prevotella intermedia*. None of these bacteria were found in the control group [24]. The presence of varicose veins is a known risk factor of DVT [38].

This preliminary study shows a relation between PD and high level of D-dimer. More prospective studies are needed to examine the possible relationship between these two disease conditions and to establish the possible pathogenic mechanisms.

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