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PhD Research

**CONTRIBUTIONS TO THE STUDY OF THE CORRELATION
BETWEEN INFLAMMATION, ATHEROGENESIS AND THROMBOSIS**

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Reason for choosing the research subject

Cardiovascular disease is associated with an increased rate of morbidity and mortality worldwide and a prevalence which increases with age. At the same time, it can be associated with different comorbidities which can contribute to the increased risk of cardiovascular disease. A patient with multiple comorbidities is challenging for the internal medicine specialist and it requires a complex approach in order to avoid further decompensation and to ensure a correct quality of life.

Periodontal disease which often has a secondary importance for the patient's doctor in the midst of other chronic diseases can induce an inflammatory systemic response leading to a decompensation of the patient's current pathology.

The present document will study in chronic inflammation generated by the periodontal disease in patients with cardiovascular disease and it also puts an emphasis on the effect of periodontal inflammation on the regulation of the coagulation process and over the atherogenesis process.

The originality of the current study stems from the evaluation of the chronic inflammatory effect over the coagulation process in patients with periodontal disease as well as measuring thrombin generation in a plasma low in thrombocytes.

We consider that our study could be useful in current medical practice, highlighting the importance of oral hygiene and oral healthcare in patients with cardiovascular disease. It also allows the further research the thrombotic risk evaluated by the production of thrombin in the presence of an inflammatory disease.

Keywords: periodontal disease, cardiovascular disease, thrombin generation, arterial stiffness, quality of life, OHIP-14

Part I.

The current state of knowledge

Periodontal disease affects the supporting structures of the teeth (namely the gingiva, the bone structure of the alveoli the periodontal ligament), which left untreated will lead to tooth loss.

(1). A healthy periodontium is defined by the absence of inflammation which is evaluated as the absence of bleeding occurring after probing or limited bleeding up to 10% of the evaluated dental sites, by the absence of clinical attachment loss and by absence of bone structure loss. (2).

We talk about periodontal disease when the gingival lesions progress to a non-reversible, chronic form, which permits bacteria to accumulate in the depth of the tissues, fact that will maintain and aggravate the inflammatory process. (1,3).

Chronic periodontitis is a disease which can occur at any age, more frequently in middle-aged individuals and the elderly (5).

In 2017, a workshop was organised in Chicago in order to optimise the diagnostic and the treatment of the periodontal disease. This workshop proposed a staging of periodontal disease according to extension severity and speed of progression. In the same time, they brought up clarifications regarding the periodontal disease in association with systemic diseases.

- | | |
|------|--|
| I. | Necrotizing periodontal disease |
| 1. | Necrotizing gingivitis |
| 2. | Necrotizing periodontitis |
| 3. | Necrotizing stomatitis |
| II. | Chronic periodontal disease |
| 1. | Stadialization after severity and complexity |
| | Stage I: initial periodontitis |
| | Stage II: moderate periodontitis |
| | Stage III: severe form with potential tooth loss |
| | Stage IV: severe form with tooth loss |
| 2. | Stadialization after extension |
| | Local |
| | Generalized |
| | Limited to molars or incisive |
| 3. | Classification after progression |
| | Grade A: slow progression |
| | Grade B: medium rate progression |
| | Grade C: rapid progression |
| III. | Periodontal disease as a manifestation of systemic disease |

Figure 1 .The 2017 classification of periodontal disease, adapted after the World Workshop on the Classification of the Periodontal and Peri-implant diseases

The periodontal disease is a public health issue, being highly influenced by poor oral hygiene, smoking and an unbalanced diet (8). A severe form of the disease is estimated to be present in 10% of the global population (9). Periodontal disease in any stage is reported to be the 11th most frequent disease with a global prevalence of 7.4% and an estimated 538 million individuals are to be affected (10, 11). The prevalence increases with age, with most of the cases been reported in individuals between the ages of 50 and 60 (12).

Although it is a very frequent disease in most countries, there are no programs dedicated to diagnosing and treating the periodontal disease (13). Furthermore, it is reported to be associated with various chronic diseases like diabetes, cardiovascular disease, obesity and metabolic syndrome further supporting the claim of being a public health, concern which merits further attention.

Concerning our country, according to the latest reports, Romania is in the 13th position in the European Union concerning individual expenditure on oral hygiene (14). There are no studies addressing the periodontal disease prevalence in Romania. There are single-center studies which report the high prevalence of periodontal disease in teenagers in Timisoara (up to 65.8%) according to Hatiegan et al. (15) According to a study of the University of Iasi, the prevalence of the periodontal disease in Romania surpasses the European average (16).

The Stability international trial (2014) which estimates the prevalence of periodontal disease in patients with cardiovascular disease and assesses the cardiovascular risk factors, reports that 49.8% of the participants in Romania have an important dental loss and the highest percentage of gingival bleeding in the participant countries (47.9%, respectively). (17)

The consensus conferences have established several recommendations regarding gingival and periodontal examination with the aim of having a rigorous and correct assessment of the periodontal disease. These recommendation need to be readily available and clear for dental healthcare professionals with various levels of expertise.

It is important to have a well established order of examination of the oral cavity in order to avoid any omissions. The examiner will note: the probing depth, alveolar bone loss, clinical attachment loss, bleeding on probing. The absence of the bleeding on probing is a good indicator for the periodontal health (2).

	Severity of the periodontal disease			
	Stage I	Stage II	Stage III	Stage IV
Probing depth	3-5 mm	5-7 mm	≥6 mm	≥6 mm
Alveolar bone loss (radiological assessment)	15%	15-30%	Extension to the 1/3 apical of the tooth	Extension to the 1/3 apical and medial of the tooth
Dental loss (periodontitis)	Absent	Absent	≤4 teeth	≥5 teeth
Clinical attachment loss	1-2 mm	3-4 mm	≥5mm	≥5mm

Table 1. Periodontal disease staging. Adapted after Tonetti et al., 2018

As well as local inflammatory changes, periodontal disease also seems to have a systemic effect, being reported as a potential risk in the pathogenesis and progression of certain chronic diseases such as diabetes, cancers, neurological diseases and cardiovascular disease. Moreover, periodontal disease also impacts the patients quality of life, being regarded as a complex disease which needs a multidisciplinary approach.

Considering the ethiopathogenetical mechanism of the periodontal disease, current research suggests that it is a chronic inflammatory disease of the periodontal tissue ,the main cause being the disruption of the oral biofilm. (115).

Bacteria being more frequently identified in the patient's oral cavity are part of the the Firmicutes, Fusobacteria, Proteobacteria, Actinobacteria ,Bacteroides, Chlamydiae and Spirochaete family (119).

Biofilm alteration can induce an immune response leading to an inflammation of the periodotium which further increases dysbiosis. Researches on inflammatory response in the presence of periodontal disease have permitted the identification of many markers present in the oral structures as well as at systemic level, shedding some light over the mechanisms involved in the development and progression of gingival disease.

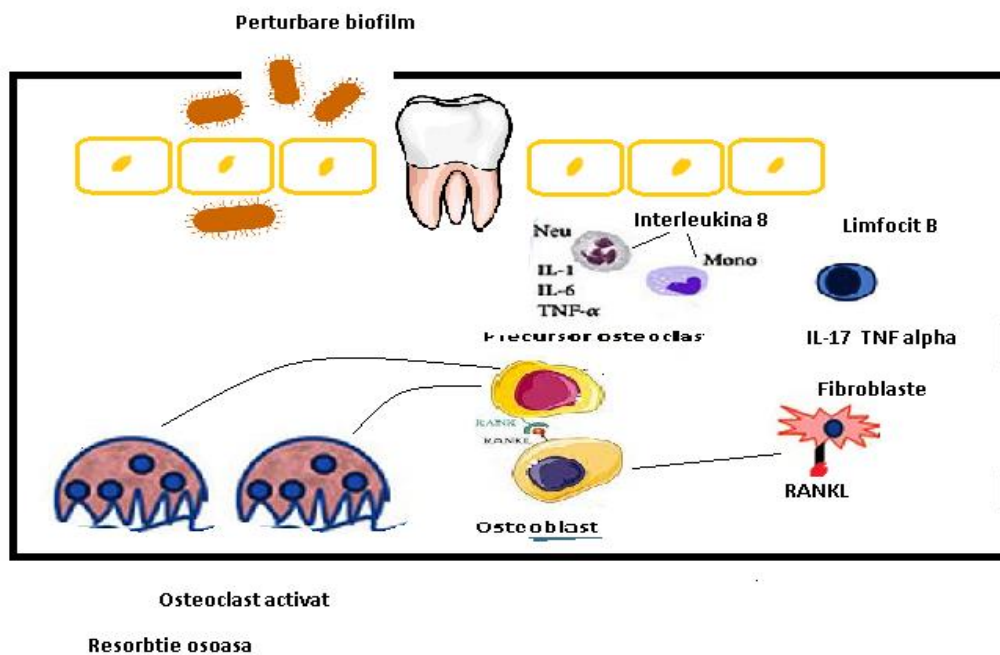


Figure 4. Periodontal disease mechanism insights

Oral pathogens (such as *P. gingivalis*, *A. actinomycetemcomitans*) are responsible for the initiation and progression of a local inflammatory process. The oral biofilm imbalance is exacerbated by the ever progressing local lesions which in turn will allow for anaerobic bacteria to colonise gingival pockets (130). Tissue damage increases the amount of crevicular fluid produced, and in its composition various molecules have been identified as being involved in inflammatory response (cellular fragments, collagen fragments, immunoglobulins, cytokines, complement and serum proteins).(27)

On top of local factors, an excessive immune response is considered to be a key factor in the development and progression of the periodontal disease (138). Amongst the pro-inflammatory cytokines there are also chemotactic cytokines (interleukine-8) which will stimulate neutrophil migration even in early stages of the disease. Cells and markers of non-specific inflammation will release enzymes and oxygen reactive species (139) which will induce further damage to the surrounding tissue, thus maintaining the inflammatory process (140).

Macrophages in turn release metalloproteinase which will break up proteins further damaging the surrounding tissue. Cytokines will stimulate the macrophage to further release metalloproteinase having a proteolytic effect on the surrounding tissue. This release of proteinase will overcome the regenerative capacity of the tissue explaining the progression of the disease (141).

At the same time, we can see a local blood vessel dilation with increasing capillary permeability with the apparition of an exudate which contains nutrients, cellular fragments and inflammatory proteins. This has a chemotactic effect on the surrounding cells recruiting more and more inflammatory cells. As an example, neutrophils recruit T and CD 17 lymphocytes which are known to be involved in bone resorption.

T-lymphocytes are part of the adaptive immune response and are involved in the local inflammatory process.

As the result of the interaction between pathogenic agents and antigen-presenting cells, T lymphocyte cells are being recruited.

Inflammatory response seems to be not only limited locally, there are numerous evidence of systemic inflammatory response which can explain the association of periodontal disease with various other other chronic diseases. For example the atherogenetic process is based on an inflammatory mechanism which leads do lipoprotein build-up in arterial walls. The inflammatory mechanism is highly complex, the mediators have a chemotactic effect on leukocytes which facilitates their infiltration in arterial walls.

Once leukocytes are inside the arterial wall they will transform in macrophage which will release cytokines and oxygen reactive species will help progress the endothelial lesion. Moreover, macrophage will phagocytate LDL-cholesterol resulting in cholesterol build up and formation of arterial plaque.

The immune response generated by periodontal disease has been associated with cardiovascular disease. Several inflammatory markers associated with periodontal disease seem to be involved in the evolution of vascular disease as well. (194, 195)

The increase in arterial stiffness is the result of the degradation of elastic fibres the proliferation of collagen fibres or both (198). Endothelial dysfunction contributes to arterial stiffness by decreasing nitrous oxide production.(199)

The gold standard technique for estimating arterial stiffness remains PWV (pulse wave velocity). Pulse wave velocity represents the velocity at which the pressure wave generated by the cardiac contraction progresses in the arteries.Changes in pulse wave velocity do not appear only in high blood pressure but have also been described in various diseases of the connecting tissue such as Marfan syndrome, diabetes and various inflammatory diseases (198). As we get older, pulse wave velocity increases resulting in a faster return of the wave to the heart during the systole. This will result in the higher systolic blood pressure with increased work and reduced coronary perfusion. (201)

At the same time inflammatory systemic inflammatory response can alter the coagulation process resulting in additional risk to patients already suffering from cardiovascular disease and endothelial dysfunction.

The analyse of the clotting process in the presence of pro-inflammatory factors, permits us to seek factors involved, thus seek better treatment of the inflammatory cause (primary prevention).

The study of thrombin generation is a method of analysing the clotting process which can evaluate the thrombotic risk by assesing the potential of the plasma to generate thrombine as a result of cascade activation of coagulation. (229)

We can follow the kinetics of the thrombin generation and we can determine several parameters (230, 231):

* Lag time is measured from the moment of adding the reactives until the first generation of thrombine (first burst).

- * Peak thrombin is the maximum concentration of generated the thrombin.
- * Time to peak is the time necessary to reach the maximum concentration of produced thrombin.
- * Velocity index or slope (peak thrombin/peak time-lag time)
- * Area under the curve is the total concentration of trombin produced in the time frame.

As the result of in systemic inflammation, periodontal disease has an effect on the evolution of cardiovascular disease. This subject is of high interest in our research field and that is why I have chosen to study patients with periodontal disease and concomitant cardiovascular disease.

Part II.

Personal contributions

Primary and secondary objectives of the research

Purpose of the research

The purpose of our research is to assess the chronic inflammation generated by the periodontal disease in patients with associated cardiovascular disease and to emphasize its effect on the coagulation and the atherogenic process.

Primary objectives of the study:

- 1/ To assess changes in salivary properties (saliva pH, saliva flow rate) in patients with periodontal disease and concomitant cardiovascular disease.
- 2/ To identify the factors that could influence the saliva properties in patients with cardiovascular disease and periodontal disease.
- 3/ To study the inflammatory response in patients with periodontal disease (by determining inflammatory markers such as c-reactive protein, IL-6 and TNF-alpha) as well as the impact of inflammatory process might have in patients with cardiovascular disease.
- 4/ To study the thrombotic risk (evaluated by determining the thrombin generation) in patients with periodontal disease and cardiovascular disease.
- 5/ To study the vascular changes in patients with periodontal disease such as arterial stiffness and atherosclerotic build-up.
- 6/ To evaluate the quality of life in patients with periodontal disease with or without associated cardiovascular disease.

Secondary objectives of the study:

- 1/ To evaluate the presence and the severity of the periodontal disease, the oral health care habits and the degree of oral hygiene in patients with cardiovascular disease.
- 2/ To evaluate the changes in salivary parameters as a result of oral hygienisation in patients with periodontal disease as well as patients with cardiovascular disease.
- 3/ To determine which cardiovascular disease is mostly associated with severe forms of periodontal disease in this study population.

4/ To evaluate thrombotic potential in conjunction with the severity of the periodontal disease.

5/ To evaluate the arterial stiffness in conjunction with in the inflammatory response generated by the periodontal disease.

6/ To highlight the importance of oral hygiene in patients with chronic diseases in current medical practice.

7/To study the impact of periodontal disease on the quality of life of patients with other associated chronic illnesses such as cardiovascular disease and to identify other factors that could impact their quality of life.

8/ To highlight the importance of an adequate oral treatment in order to prevent and/or reduce any systemic effect of oral diseases.

Research methodology. Ethical considerations

We conducted this study between June 2018 and December 2020, being approved by the Ethics Committee of the Emergency County Hospital in Sibiu (approval number 10936 / 25.05.2018).

Clinical studies were conducted according to a research protocol developed in conformity with National and International requirements in the field of medical research on human subject as well of the Declaration of Helsinki. Subjects were included after being explained the terms and conditions of participating in this study, they have all signed an informed consent declaration.

Patient and personal data confidentiality has been guaranteed. A study protocol has been developed and the inclusion and exclusion criteria were thoroughly respected.

Patients were recruited in the study from the Emergency County Hospital in Sibiu, from the Cardiology and Oral Health departments.

Statistical analysis

Patients were included in Excel databases and the information obtained was analysed. In order to preserve the personal data confidentiality, an unique code was attributed to each patient.

Statistical analyses were performed using SPSS version 17. For numeric variables, descriptive statistics were performed, and the comparisons between these variables were made with the nonparametric Kruskal-Wallis test for more than 2 independent series and with the Mann-Whitney U test for comparisons between 2 sets of independent values with no Gaussian distribution. For comparisons between 2 paired numerical series, the Wilcoxon signed-rank test was used. The correlations between numerical variables were made by determining the Spearman's correlation coefficient. Results were considered significant with a value of $P < 0.05$

Study 1. Assessment of salivary properties in patients with periodontal disease

1.1. Introduction

Saliva has an important role in maintaining the oral health (169), one of the mechanisms being the permanent adjustment of the pH (168). The salivary secretion and its composition depend of multiple factors such as age, gender, body mass index (211) the patient's medication (34) and last but not least, of the oral hygiene habits. Any modification of the saliva properties is prone to induce oral health issues, such as plaque, dental caries, gingivitis and even periodontal disease (242).

Saliva is an useful analysis liquid being available in larger amounts than crevicular fluid and it can be prelevated several times without inducing trauma to the patient (245). Moreover, we can use it to identify multiple markers that are generated by the oral biofilm alteration or the patient's oral health issues.

The study's purpose is to evaluate the salivary modifications (saliva pH and salivary flux variations) in patients with periodontal disease with or without cardiovascular disease. As it follows, our specific purpose is to:

- evaluate the presence, the severity of the periodontal disease and the oral hygiene habits of the patients with cardiovascular disease;
- identify the factors that could influence the saliva modifications in patients with cardiovascular and periodontal disease ;
- to assess the saliva changes after performing a thorough oral hygienisation

1.2. Materials and method

The study took place between June 2018-December 2019, under the supervision of the Ethical Committee of The Emergency County Hospital Sibiu (approval number 10936/25.05.2018).

The patients were selected after thoroughly applying the inclusion and exclusion criteria and a total of 155 subjects were included. Their medical charts were used to obtain the necessary information regarding their associated diseases and their chronic treatment. The weight and height were measured for all patients, permitting thus the BMI calculation.

A questionnaire was given to all patients in order to evaluate the oral hygiene habits (dental brushing, mouthwash use, dental flossing and visits to the oral healthcare provider), their eating habits and the physical exercise level. Afterwards, an oral examination was performed and the presence of the periodontal disease and its severity was noted according to the consensus recommendations published in 2018(2). The oral healthcare provider also noted the

oral hygiene level by calculating the hygiene score Oral health index simplified (OHI-S) (251). Saliva pH and saliva flow rate were measured for each patient and afterwards an oral hygienisation was performed. Three months after the oral hygienisation process, the saliva parameters were measured again and compared to the first values obtained.

1.3. Results

From the total of the 155 patients (50.3% men and 49.7 % women), with an average age of 64.49 ± 14.72 years, 102 (65.8%) had periodontal disease.

Older patients seem to have more severe forms of periodontal disease ($p < 0.001$, Kruskal-Wallis). In the same time, severe forms of periodontal disease were found in obese patients and in those having an associated cardiovascular disease ($p < 0.001$). Patients with tooth loss ($p = 0.001$) and with a low oral hygiene score ($p = 0.002$). As expected, bleeding on probing is more frequent in patients with periodontal disease, but it is also present in patients without periodontal disease. A good oral hygiene, meaning regular oral hygienisation, mouthwash use and dental flossing is associated with the absence of periodontal disease ($p = 0.003$, $p = 0.002$ și $p = 0.005$, respectively). Moreover, the presence of dental plaque seems to be a significant risk factor for periodontal disease (Chi² Test, $p = 0.046$, OR=2.01, 95%CI=[1.02, 3.93]).

Patients have significant changes in saliva pH and the saliva flow rate three months after the oral hygienisation.

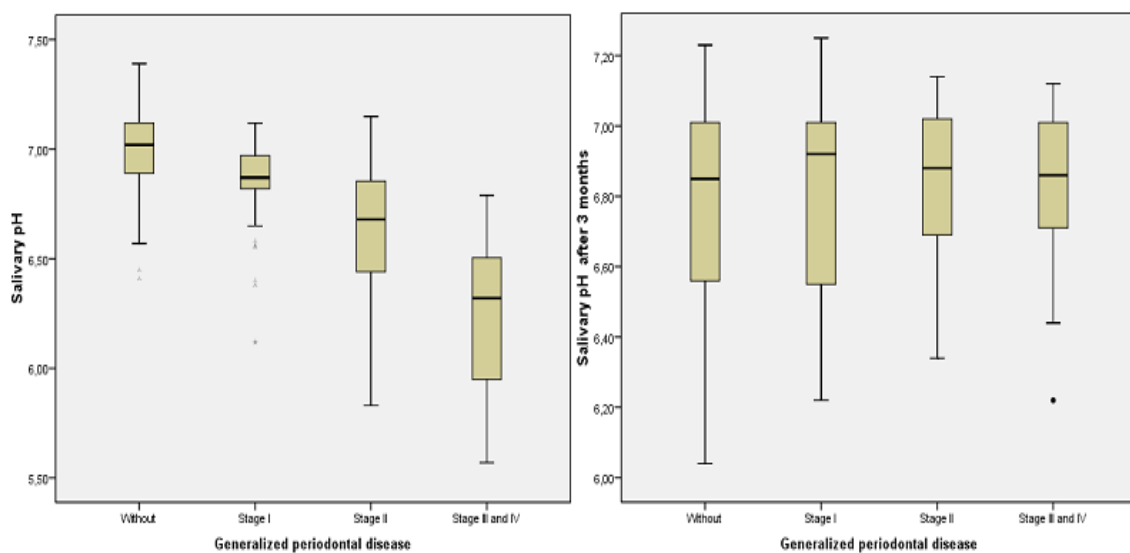


Figura 9: Saliva pH changes three months after dental scaling

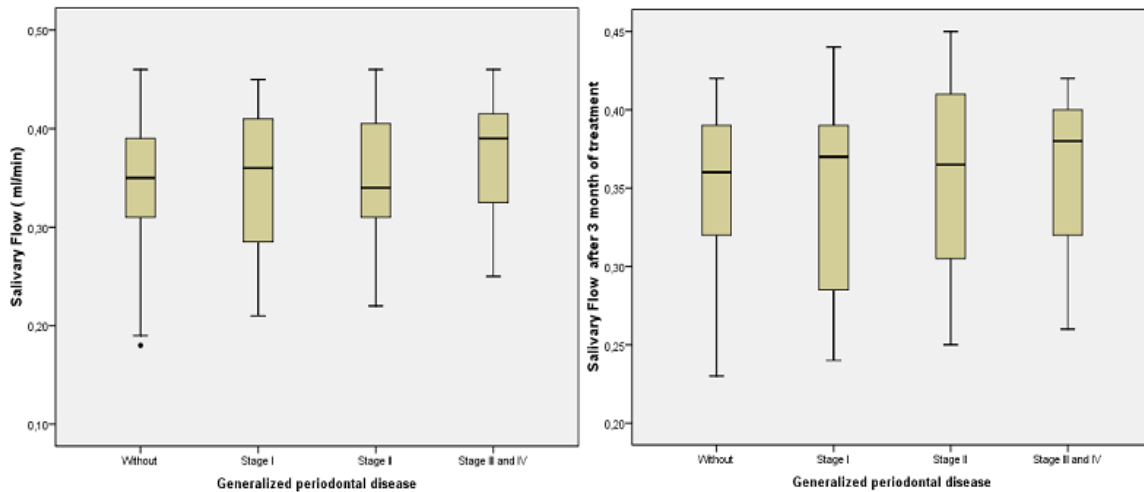


Figura 10: Saliva flow rate evolution three months after dental scaling

In total, 78.7% (122) of patients included in the study had cardiovascular disease. All had hypertension under treatment, and some patients had other associated cardiovascular diseases: 61.67% had stable coronary disease and 45.8% had myocardial infarction. In addition, 60.75% had degenerative valvular disease and 20.8% had arrhythmia. All patients with periodontal disease had a significantly higher prevalence of arrhythmia ($P=0.01$), peripheral artery disease, and coronary disease ($P=0.032$). The association between valvular disease and the presence of periodontal disease (regardless of the severity) was nonsignificant ($P=0.23$). Arrhythmia and myocardial infarction at a younger age (<60 years) was more frequent in patients with a severe form of periodontal disease (6.4% and 2.4%, respectively). All patients with severe forms of periodontal disease had an associated cardiovascular disease (Figure 11).

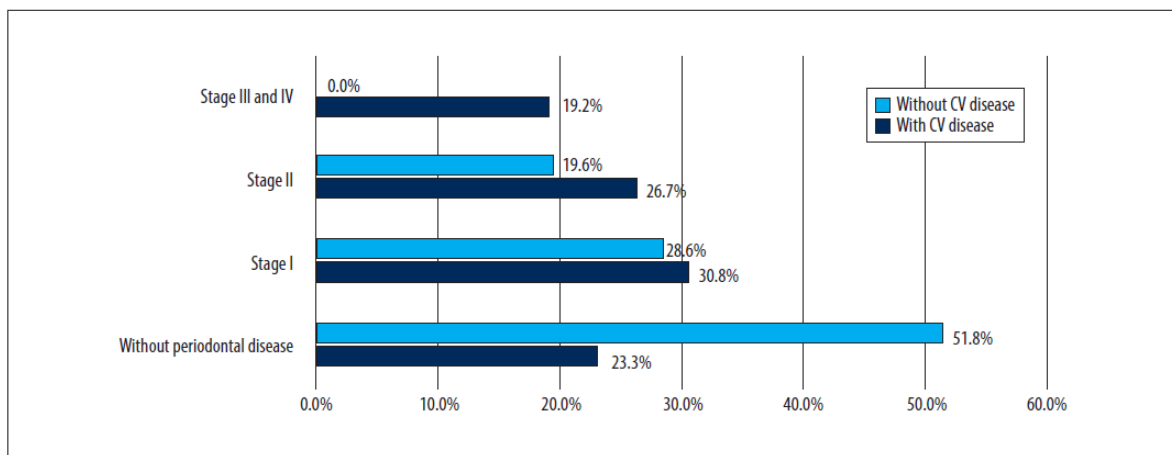


Figura 11 : Relationship between cardiovascular disease and periodontal disease severity (CV= cardiovascular)

By conducting logistic regression analysis with cardiovascular disease as a dependent variable, we observed that poor dental hygiene (as evaluated with the OHI-S score) was a significant risk factor for cardiovascular disease. Moreover, clinical attachment loss was a risk factor for cardiovascular disease, and an increased saliva flow rate had a protective role.

1.4. Conclusions

1. Patients with severe forms of periodontal disease have lower saliva pH and a lower saliva flow rate.
2. A low saliva pH is associated with alcohol consumption, obesity/ overweight and with tooth loss. The saliva pH decreases with the increase of the severity of periodontal disease.
3. The low saliva flow rate is associated with smoking, obesity/overweight and with tooth loss. In the meantime, it also decreases with the increase of periodontal disease severity.
4. Saliva parameters are significantly improved three months after oral hygienisation was performed.
5. The severity of periodontal disease is associated with a poor oral hygiene; an adequate oral healthcare could have a protective role in the appearance and progression of periodontal disease.
6. Severe forms of periodontal disease are associated with acute cardiovascular events, such as arrhythmia and acute myocardial infarctus, which tend to appear earlier in patient's life.
7. The patients with cardiovascular disease included in the study tend to have poor oral hygiene.
8. By increasing the population awareness concerning the importance of the oral hygiene, we could obtain better results in treating and preventing periodontal disease and thus eventually prevent acute cardiovascular events.
9. Further studies to assess chronic diseases impact on oral hygiene are necessary. In the same time, the oral healthcare provider is an important asset in supervising patients with multiple comorbidities.

8. Saliva pH and saliva flow rate could be used as potential markers in the follow-up of patients, being cheap and easy to evaluate in a dental practice by the oral healthcare professional.

Study 2. Evaluation of the potential thrombotic risk in patients with periodontal disease

2.1. Introduction

Periodontal disease could have a systemic effect, being associated with different chronic diseases (such as diabetes, cancer, cardiovascular disease), but until now, there is no established causal relationship between them. (278,279).

Some authors admit a potential thrombotic risk in patients with periodontal disease; there are case-reports of deep vein thrombosis and pulmonary embolism in the context of severe forms of periodontitis(239,280). It is not known yet how periodontal disease could induce thrombosis, but it is suspected that systemic inflammatory response associated with the gingival inflammation could explain the thrombocytes activation and generate the thrombotic process.(240,281)

The chronic inflammation induces an endothelial dysfunction and thus permitting the thrombin activation and initiating the coagulation process (283. The Prosper study evaluates the relationship between the inflammatory markers and the thrombin generation process, proving an increase of thrombin generation in an inflammatory context (286). In patients with cardiovascular disease, an association between a higher mortality rate and the increase of the parameters of thrombin generation was reported (285),

Until now, there are no studies to assess the effect of the periodontal disease in thrombin generation in patients with cardiovascular disease.

Our study's purpose is to explore the thrombin generation and the systemic inflammation in patients with periodontal disease and cardiovascular disease, in order to evaluate the potential thrombotic risk in these subjects.

2.2. Materials and methods

The study took place between June 2018-December 2020, under the supervision of the Ethical Comitee of The Emergency County Hospital Sibiu (approval number 10936/25.05.2018).

All participants gave their signed consent in order to participate and after applying the inclusion and the exclusion criteria, a total of 90 patients from the Cardiovascular Unit of the Emergency County Hospital Sibiu were selected. Each subject was examined by an oral healthcare provider in order to establish the presence and the severity of the periodontal disease and afterwards, blood samples were taken for analysing the systemic inflammation (C reactive protein, fibrinogen, interleukin -6 and tumour necrosis factor alpha) and the thrombin

generation process. Other blood tests (such as blood count, blood sugar and cholesterol level) were obtained from each patients' medical chart.

2.3. Results

The study includes a total of 90 patients with cardiovascular disease with an average age of 67.93 ± 10.54 years and an equal sex repartition (50% men, 50% women), majoritary from an urban area (56.73%).

Obesity and overweight are significantly associated with the presence of periodontal disease; an increased BMI is a significant risk factor for severe forms of periodontal disease (OR=1.15 cu 95% C.I. pentru OR=[1.007, 1.314]). Furthermore, the cholesterol levels (total cholesterol and LDL) are significantly higher in patients with periodontal disease (Mann-Whitney test, $p < 0.001$ and 0.046 , respectively).

IL-6 și TNF-alpha levels are higher in patients with periodontal disease, increasing with the severity of the periodontitis (Mann-Whitney, $p < 0.001$).

Considering the thrombin generation, the area under the curve (endogen thrombinic potential) is not increased in obese patients (Mann-Whitney, $p = 0.099$), but the Peak values are significantly increased in overweight and obese patients (Mann-Whitney, $p = 0.025$).

The Time to lag and Time to peak values are significantly lower in patients with periodontal disease (Mann-Whitney U Test, $p < 0.001$) showing a faster thrombin generation in this case. Furthermore, the velocity index, Peak and area under the curve are significantly higher in the group of patients with periodontal disease.

The area under the curve and the Peak values are also correlated with the inflammatory markers determined in these patients, as seen in table 9.

		Peak	AUC
IL-6	Pearson	0.359**	0.382**
	Sig. (2-tailed)	0.001	<0.001
TNF-alpha	Pearson	0.297**	0.283**
	Sig. (2-tailed)	0.004	0.007

Table 9. Correlations between the inflammatory response and thrombin generation

2.4. Conclusions

1. Obesity and overweight are significantly associated with the presence of the periodontal disease; a higher BMI is a significant risk factor for periodontal disease.
2. The total cholesterol and LDL- cholesterol values are significantly higher in patients presenting both cardiovascular and periodontal disease.
3. IL-6 and TNF-alpha levels are increased in patients with periodontal disease. .
4. Obese patients have higher Peak values in the thrombin generation process, although the area under the curve does not follow this trend.
5. The area under the curve and the Peak values are significantly correlated with the inflammatory markers (TNF- α and IL-6).
6. Velocity index, Area under the curve and Peak values are significantly higher in patients with cardiovascular and periodontal disease, in comparison with the group of patients with cardiovascular disease but no periodontal disease.
7. The periodontal disease, looked-upon as a chronic inflammatory disease, could have an influence on the thrombin generation and to induce a thrombotic risk in this group of patients.
8. An adequate evaluation of patients with oral health issues could allow an early identification of patients with a thrombotic risk especially in the context of the presence of other chronic diseases such as cardiovascular disease.

Study 3. Evaluation of atherogenesis process in patients with periodontal disease

3.1. Introduction

Periodontal disease might have an inflammatory systemic impact, according to studies which implicates it in the development of the atherogenetic process (290). The observational studies assessing patients with periodontal disease suggest that there is a linear relationship between the periodontal disease and the atherosclerosis progression (evaluated through carotid ultrasound) (294,295), the severity of the periodontal disease being significantly correlated with the systemic inflammation and the intima-media index (296). Interventional studies on patients with periodontal disease show a promising effect regarding the atherosclerosis progression with a better disease control (298).

The purpose of this study is to identify the modifications of the intima-media index and to evaluate the arterial stiffness in patients with periodontal disease and cardiovascular disease.

3.2. Materials and method

The study took place between June 2018-December 2019, under the supervision of the Ethical Comitee of The Emergency County Hospital Sibiu (approval number 10936/25.05.2018). After applying the inclusion and exclusion criteria, a total of 104 patients were selected from the Cardiology Unit and the Oral Health Department of the Emergency County Hospital Sibiu to study the impact of the periodontal disease on the arterial stiffness and carotid ultrasound modifications.

All patients underwent the following exams: an oral health examination, blood tests in order to determine the systemic inflammatory response, the evaluation of the arterial stiffness and a carotid ultrasound.

Considering the presence of the periodontal and the cardiovascular disease, we obtained three groups of patients that were subsequently compared: Am obținut 3 loturi de pacienți, în funcție de prezența bolii parodontale și a bolii cardiovasculare care au fost comparate ulterior:

- * group 1 : patients with cardiovascular disease (N=41);
- * group 2 : patients with both cardiovascular and periodontal disease (N=33);
- * group 3 : patients with periodontal disease (N= 30).

3.3. Results

The study includes a total of 104 patients with an average age of 67.93 ± 10.54 years, the majority from an urban environment.

The patients with periodontal disease and associated cardiovascular disease are overweight or obese, their BMI is higher than that of the patients without periodontal disease ($p=0.01$, Kruskalis Wallis). Most of patients with periodontal disease are active smokers (35.5% of the total of patients).

More severe forms of periodontal disease were found in patients with associated periodontal disease.

The inflammatory markers (C reactive protein, IL-6 and TNF-alpha) are higher in patients with periodontal disease (Mann-Whitney U, $p < 0.001$) and there are no significant differences between the study groups regarding the fibrinogen levels.

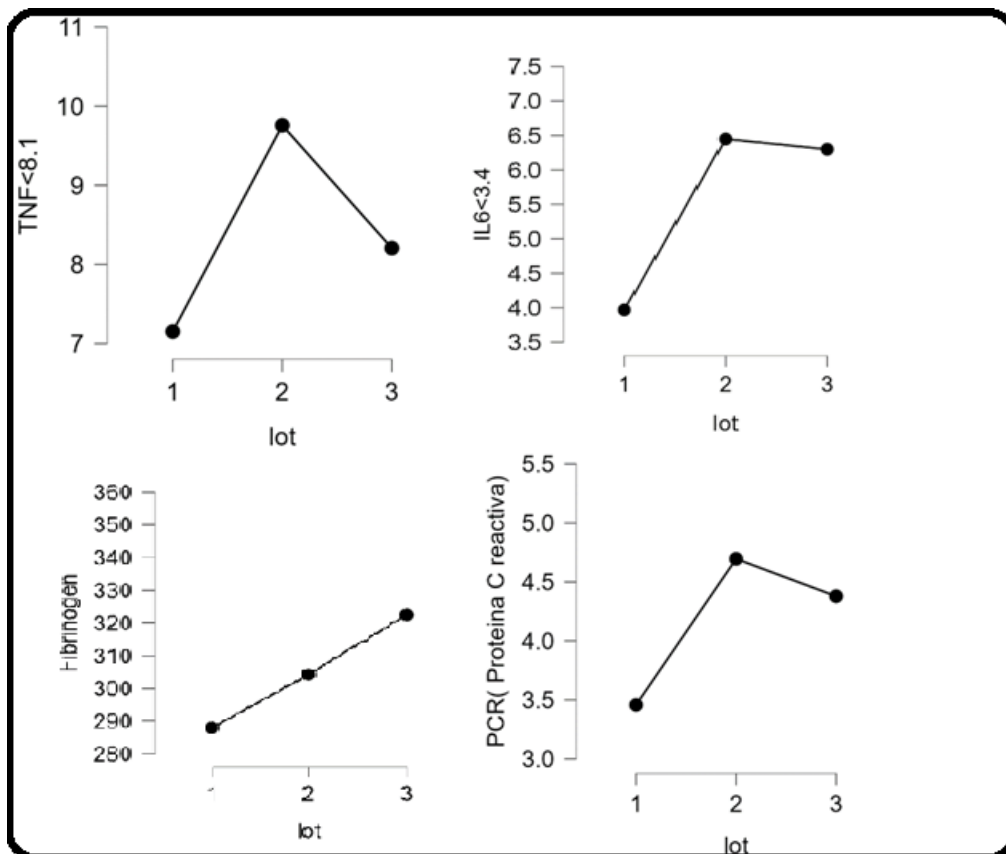


Figure 16. Comparison of the inflammatory markers between the three groups of patients (TNF alpha, IL-6, Fibrinogen, C reactive protein)

The values of the arterial rigidity parameters are significantly increased in patients with periodontal disease and associated cardiovascular disease. The patients who have only

periodontal disease also have higher values of these parameters than patients with only cardiovascular disease

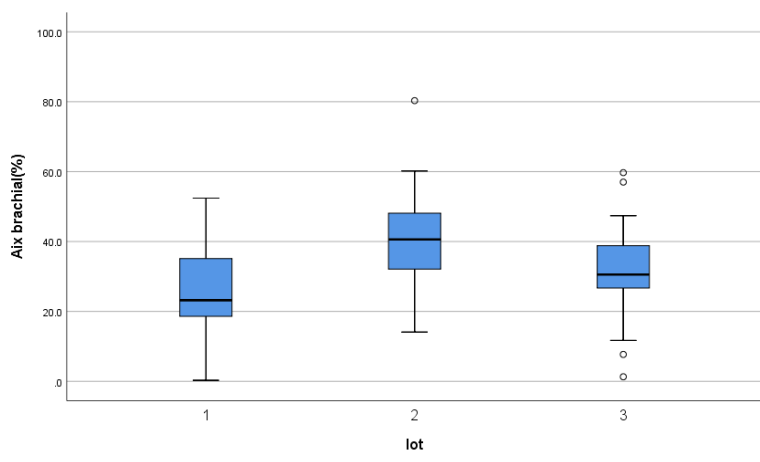


Figure 17. Comparison of the arterial stiffness measurements (Aix brachial) between the three groups of patients

The value of the pulse wave velocity (PWW Ao), Aix Ao si Aix brachial ar significantly higher in the context of periodontal disease (Mann-Whitney U test, $p < 0.001$). Periodontal disease is more frequent in patients from the urban area. (χ^2 test, $p < 0.001$).

Concerning the carotid ultrasound exams, the mean value of the intima-media index is $0,695 \pm 0,24$ mm. We obtained strong and significant correlations between the intima-media index and the total cholesterol values ($p = 0,01$, Kruskal Wallis) and the LDL-cholesterol values ($p = 0,02$, Kruskal Wallis). The correlation between the intima-media index and the systolic blood pressure values are weak, but significant ($p = 0,05$).

The intima-media index has significantly higher values in patients with periodontal disease and associated cardiovascular disease ($p = 0.01$, Kruskal Wallis). In the same time, atheromatous plaques/calcifications are more significant in patients with periodontal disease ($p = 0.019$, Kruskal Wallis).

4.4. Conclusions

1. In patients with periodontal disease the augmentation index (indicator of endothelial dysfunction) and the pulse wave velocity (indicator of arterial stiffness) are significantly higher than in patients with cardiovascular disease with no associated periodontal disease.

2. The values of the C reactive protein, IL-6 si TNF-alpha are significantly higher in patients with periodontal disease; the values increase with the severity of the periodontal disease.
3. There is a correlation between the periodontal disease, the systemic inflammatory response and the arterial stiffness in this group of patients.
4. The intima-media index is significantly higher in patients with cardiovascular and associated periodontal disease. In the same time, the periodontal disease is associated with the presence of the atheromatous plaque.
5. The presence of the periodontal disease might be an incentive to study the arterial stiffenss in ordere to have a better view over the global cardiovascular risk.
6. The periodontal disease is a potentially modifiable risk factor. By efficiently treating and preventing the aggravation of the gingival lesions, we could contribute to a better control of the inflammation and prevent its systemic effects.
7. The presence of the periodontal disease (especially the severe forms of periodontal disease) in patients with cardiovasular disease could induce a supplementary risk in the apparition of the acute cardiovascular events.

Study IV. Quality of life in patients with periodontal disease and cardiovascular disease

4.1. Introduction

Periodontal disease causes gingival alterations as well as a destruction of the support structures of the teeth(27) and in the same time it is also believed to have a potential systemic effect by generating an inflammatory response which in turn could influence other chronic diseases(137). Patients with periodontal disease tend to have a lower quality of life (310) and in the context of the presence of other comorbidities, oral health care does not seem to be a priority for these patients(311). Even if periodontal disease can be treated effectively and safely by an oral health care specialist (313), patients have a tendency to fail seeking adequate treatment (314), leading to a low oral health-related quality of life.

The aim of this study is to evaluate factors that could influence the quality of life in patients with periodontal disease and concomitant cardiovascular disease, by applying the OHIP- 14 questionnaire.

4.2. Materials and methods

This study was conducted between June 2018 and December 2019 at the Sibiu Emergency County Hospital. The study protocol was evaluated and approved by the Ethics Committee of the hospital (approval number 10936 /25th of May 2018).

Patients were recruited according to inclusion and exclusion criteria from the Cardiology and Oral Health Departments of the hospital. A total of 221 patients were included in the study. Each patient was subject to an oral cavity exam which allowed to assess the presence and the severity of the periodontal disease. Afterwards, patients were asked to fill the OHIP-14 questionnaire. The OHIP-14 general score was calculated as well as the subdomain scores, thus allowing further comparison with other variables.

4.3. Results

We have included a total of 221 patients aged between 25 and 92 years with a mean age of 61.86 ± 15.03 years, 51.14% women and 48.86% men. Of the total of 221 patients, 66.5% had cardiovascular disease. Oral examination showed that 131 patients (59.3% respectively) had periodontal disease (27.6% first stage, 21.3% second stage 10.4% stages 3 and 4). OHIP-14 score varied between 2 and 36 points with a mean value of 12.5 ± 9.1 .

In univariate analysis, age, BMI and the number of missing teeth are all factors that significantly influence the quality of life in these patients. Furthermore, we noticed

significant differences between age groups, patients over 70 years have an OHIP-14 score above the groups average, 17.17 respectively ($p < 0.001$).

No significant differences were found in the general OHIP-14 score in patients from urban environment or rural environment ($p = 0.339$), nor have we found any significant differences between men and women ($p = 0.63$). Alcohol and tobacco consumption do not appear to have an influence on the quality of life.

Dental disease has an impact over the perception of oral health related quality of life as shown by the results of variance analysis [$F(3,216) = 1071.9, p = 0.0001$]. The impact periodontal disease diagnosis over the quality of life is highly significant (eta squared partial 0.937).

We also obtained significant differences concerning the quality of life score in patients with different stages of periodontal disease, meaning that the patients with severe forms of periodontal disease have a lower oral health-related quality of life than the rest of the groups. Patients with cardiovascular disease have a lower quality of life than those without associated cardiovascular disease ($p < 0.001$ with 22% association, ANOVA). Patients having both cardiovascular and periodontal disease experience a significant lower quality of life ($p < 0.001$, ANOVA), as seen in Figure 20.

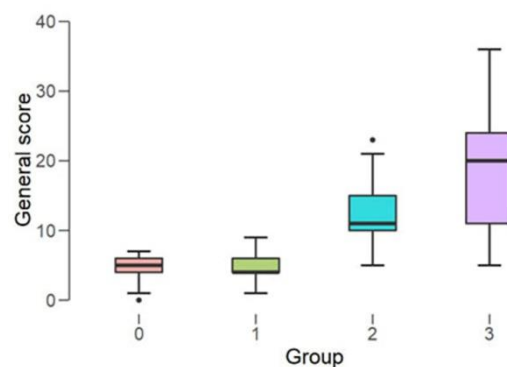


Figure 20. Periodontal disease and cardiovascular disease in association with the OHIP-14; Group 0: no cardiovascular and no periodontal disease; Group 1: cardiovascular disease (N=147); Group 2: periodontal disease (N=131); Group 3: Cardiovascular and periodontal disease (N=114). The dots (group 0 and group 2) mark the extreme values of the general OHIP-14 score (0 and 23, respectively).

By analysing each OHIP-14 domain, patients included in the study scored highest in Pain, Functional limitation and Functional disability and experienced a lower impact of Psychological discomfort on the quality of life (**Table 17**).

OHIP-14 domains	Mean ± SD
Functional limitation	2.15 ± 1.55
Pain	3.09 ± 1.81
Psychological discomfort	1.69 ± 1.56
Physical disability	2.09 ± 1.98
Psychological disability	0.82 ± 1.3
Social handicap	1.13 ± 1.28
Handicap	1.45 ± 1.23

Table 17. Domain OHIP-14 mean scores per domain in all patients included in the study

4.4. Conclusions

1. The severity of the periodontal disease is associated with a lower oral health-related quality of life.
2. The presence of cardiovascular disease as a comorbidity lowers the quality of life in patients with periodontal disease; although the OHIP-14 score obtained is lower compared to European average, periodontal disease and cardiovascular disease both have a significant impact on the quality of life in the study group.
3. Patients with cardiovascular and periodontal disease both have a low quality of life with higher scores especially in the subdomains of pain and functional limitation.
4. In the univariate model of statistical analysis, age, BMI, smoking, poor oral hygiene, tooth loss were all associated with a lower quality of life. Multivariate statistical analysis shows an important impact of age, BMI and oral hygiene (dental floss) on the quality of life of individuals.
5. Patients seem to have an insufficient level of knowledge regarding oral hygiene. We consider that the OHIP-14 questionnaire is useful in helping patients as well as their oral

hygiene specialists to identify specific problems which could have an impact on the quality of life.

6. We emphasise the importance of rigorous oral hygiene in patients chronic illnesses as well as the importance of a multidisciplinary approach (attending doctor, healthcare specialist) to improve ones health status and to improve the quality of life .

General conclusions

1. Severe forms of periodontal disease bring about changes in salivary parameters with lower pH values and a lower rate of salivary flow rate.
2. A low salivary pH is associated with alcohol consumption, obesity, cardiovascular disease risk factors, pH values are inversely correlated with periodontal disease severity.
3. A low salivary flow rate is associated with active smoking, obesity and with tooth loss meanwhile the flux of the saliva decreases with the severity of periodontal disease.
4. Oral health care in periodontal disease brings about significant improvement in salivary parameters.
5. Saliva pH and the saliva flow rate are easy to measure and the oral healthcare provider could use them to monitor patients in his practice.
6. Poor oral hygiene (as evaluated by the OHI-S score) is associated with severe forms of periodontal disease it is also a significant risk factor for cardiovascular disease. By increasing the awareness of oral hygiene we could improve patient outcomes in periodontal disease which in turn could contribute to preventing acute cardiovascular events.
7. Myocardial infarction and arrhythmia are more frequent in patients with severe forms of periodontal disease.
8. IL-6 and TNF- α values are significantly increased in patients with periodontal disease values which correlate with the severity of the disease.
9. Periodontal disease as seen as a chronic inflammatory disease can increase the thrombotic risk by influencing thrombin generation. Adequate work-up of individuals with periodontal disease could allow for the evaluation of patients at thrombotic risk.
10. The thrombin generation parameters, area under the curve (endogenous thrombinic potential) and Peak value are significantly correlated with the inflammatory markers (TNF- α and IL-6).
11. The Velocity index, area under the curve and Peak values are significantly higher in patients with cardiovascular disease and associated periodontal disease than in patients presenting only cardiovascular disease.

12. Total cholesterol and LDL-cholesterol are significantly higher in patients with periodontal disease. Obesity is also significantly associated with the presence of periodontal disease, a higher BMI is a risk factor for periodontal disease.
13. Periodontal disease seems might increase the risk of cardiovascular disease by inducing arterial stiffness which is considered as a marker of subclinical atherosclerosis.
14. Gingival disease seems to alter the arterial stiffness, as proven by the Arteriograph enregistrement, with increased values of the augmentation index and pulse wave velocity.
15. The presence of periodontal disease is an indication to study arterial stiffness in order to evaluate global cardiovascular risk these patients might be a target for primary prevention.
16. Severe forms of periodontal disease are associated with significant changes in carotid intima-media thickness.
17. Prophylactic measures could be implemented in order to prevent severe forms of periodontal disease by reducing systemic and local inflammation.
18. The presence of periodontal disease lead to low quality of life; the more severe the disease is, the lower the quality of life.
19. Age, oral hygiene and BMI have an impact on the oral health-related quality of life in patients.
20. Patients with cardiovascular and periodontal disease both have a low quality of life with higher scores especially in the subdomains of pain and functional limitation.
21. Patients seem to have an insufficient level of knowledge regarding oral hygiene; the OHIP-14 questionnaire is useful in helping patients as well as oral hygiene specialists identify specific problems which could have an impact on the quality of life.
22. We emphasise the importance of rigorous oral hygiene in patients chronic illnesses as well as the importance of multidisciplinary approach (attending doctor, healthcare specialist) to improve ones health status and to improve the quality of life.
23. Studies are necessary to assess the impact of chronic diseases on oral health; the oral healthcare specialist is an important partner in the care of patients with complex comorbidities.

Elements of originality

1. It is the first study in our country to assess the potential thrombotic risk in patients with periodontal disease and associated cardiovascular disease, by determining the thrombin generation parameters. We also evaluated the inflammatory syndrome generated by the periodontal disease and its effect on the thrombin generation and the arterial stiffness.
2. It is the first study in our country to contribute to the identification and the characterisation of the cardiovascular risk factors implicated in the apparition and the progression of the periodontal disease.
3. We had a multidisciplinary approach of the periodontal disease with the collaboration of the internal medicine specialist, the oral healthcare provider, the cardiologist and the laboratory specialist doctor.

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