PERIODONTITIS AND THE ATHEROSCLEROTIC CORONARY CARDIOVASCULAR DISEASE. COMPARATIVE STUDY OF SYSTEMIC INFLAMMATION - PERIODONTITIS - IN CARDIOVASCULAR DISEASE ON A STUDY GROUP OF 916 PATIENTS

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Abstract: *Recent parodontology studies claim that periodontal disease causes predisposition to atherosclerotic cardiovascular disease on account of some derived pro-inflammatory local and systemic reactions similar to atherosclerosis and consisting of cytokines produced by monocytes and other inflammatory intermediaries induced by periodontal pathogens and by their endotoxin, lipopolysaccharide. This mechanism may initiate vascular endothelial dysfunction with its implications in atherosclerosis and in atheromatous plaque inflammation. Inflammation is the physiopathological link between periodontitis – atherosclerosis – cardiovascular disease and it all links obsessively starting with hygiene, more specifically oral hygiene, chronic bacterial infection, gingivitis – periodontitis – local and systemic inflammation. Following the potential risk and the inflammatory connections between the periodontal disease and the complications of cardiovascular coronary disease we may draw a few conclusions based on our investigations. The inflammatory connections between the two affections are made through common pro-inflammatory markers such as C-reactive protein, different cytokines secreted both at local inflammation level as well as at systemic inflammation level, different cytokines present at the level of atherosclerotic plaque or clinically deduced at the level of endoarterial epithelium. A series of studies claim the predictive value of C-reactive protein taken at admission of the coronary patient and its dynamic monitoring during hospitalization, correlated as maximum value at CK-MB enzyme and LDH peak level. Out of the numerous inflammatory markers studied for their potential risk factor role, C-reactive protein has the best laboratory test performance and presents the strongest association with cardiovascular events. Plasmatic C-reactive protein is produced by hepatocytes under transcriptional control of pro-inflammatory cytokine (IL-6, IL-1, alpha TNF). The plasmatic level of C-reactive protein may be highlighted at 4 hours after tissues injury, since it increases 1000 times in 24-27 hours. Serum level of C-reactive protein directly reflects the intensity of the pathological process that stimulated its production. C-reactive protein is also known as the "pro-inflammatory protein" due to its ability to stimulate complement activity in defence of the host and to mediate fagocitosis. C-reactive protein induces monocyte production of tissue factor, a pro-coagulant playing a key role in arterial thrombosis. Examination results at all four groups of patients in our study support the mechanisms of the local and systemic pro-inflammatory reactions, derived from the host, similar to atherosclerosis and consisting of cytokines produced by monocytes and other inflammatory intermediaries induced by periodontal pathogens and by their endotoxins. These mechanisms may be the start of vascular endothelial dysfunction and ulterior sequelae leading to atherosclerosis with its complications. Clinical evidence expressed through umoral markers show the determination between the local and the systemic inflammation as a result of localized chronic infection. Alteration of the levels of inflammatory intermediaries has a significant impact on the atherosclerotic processes associated with the inflammation.*

Keywords: *Periodontitis, inflammation, C-reactive protein*

Rezumat: *Cercetările recente în parodontologie sugerează că boala periodontală predispune la boala cardiovasculară aterosclerotică pe baza unor reacţii pro – inflamatorii locale şi sistemice derivate similar aterosclerozei şi constând din citokine elaborate de monocite şi alţi intermediari inflamatori care sunt induşi de patogeni periodontali şi edotoxina acestora, lipopolizaharidul. Prin acest mecanism s-ar putea iniţia disfuncţia endotelială vasculară cu urmările sale asupra aterosclerozei şi plăcii ateromatoase care are la bază inflamaţia. Inflamaţia este firul ce leagă fiziopatologic periodontita – ateroscleroza – boala cardiovasculară şi obsedant, totul se înlănţuieşte pornind de la igienă, respectiv sănătatea orală, infecţia bacteriană cronică, gingivita – periodontita – inflamaţia locală şi cea sistemică. Urmărind riscul potenţial şi conexiunile inflamatorii dintre boala periodontală şi complicaţiile bolii cardiovasculare coronariene, putem constata pe*

baza rezultatelor din investigaţiile noastre mai multe aspecte. Conexiunile inflamatorii dintre cele două afecţiuni sunt realizate prin markeri pro-inflamatori comuni, cum sunt proteina C-reactivă, diferitele ciokine secretate atât la nivelul inflamaţiei locale, cât şi la nivelul inflamaţiei sistemice cele de la nivelul plăcii aterosclerotice sau a epiteliului endoarterial deduse clinic. O serie de studii susţin valoarea predictivă a proteinei C-reactive prelevată la internarea bolnavului coronarian şi urmărirea acestuia în dinamică în timpul spitalizării, care se corelează ca valoare maximă în momentul de vârf al nivelului enzimei CK-MB şi ale LDH. Din numărul mare de markeri inflamatori studiaţi pentru rolul lor potenţial de factori de risc, proteina C-reactivă posedă cele mai bune performanţe a testelor de laborator şi prezintă cea mai puternică asociere cu evenimentele cardiovasculare. Proteina C-reactivă plasmatică este produsă de către hepatocite sub controlul transcripţional al citokinei pro-inflamatorii (IL-6, IL-1, TNF alfa). Nivelul plasmatic al proteinei C-reactive poate fi pus în evidenţă la 4 ore după injuria ţesuturilor, sporind de 1000 de ori în 24-27 ore. Nivelul seric al proteinei C-reactive reflectă direct intensitatea procesului patologic care i-a stimulat producţia. Proteina C-reactivă mai este cunoscută şi sub denumirea de "molecula efectoare pro inflamatorie" datorită abilităţii sale de a stimula activitatea complementului în apărarea gazdei şi de a media fagocitoza. Proteina C-reactivă induce producţia de către monocite a factorului tisular, un pro-coagulant cu rol cheie în tromboza arterială. Rezultatele examinărilor celor patru grupuri de bolnavi din studiul nostru susţin mecanismele reacţiilor pro-inflamatorii locale şi sistemice, derivate din gazdă, similare aterosclerozei constând din citokine derivate monocitic şi alţi intermediari inflamatori care sunt induşi de patogenii periodontali şi endotoxinele lor. Aceste mecanisme ar putea constitui startul disfuncţiei endoteliale vasculare şi sechele ulterioare ducând la ateroscleroză şi complicaţiile ei. Dovezile clinice exprimate prin markeri umorali evidenţiază determinarea dintre inflamaţia locală şi cea sistemică urmare a infecţiei cronice localizate. Modificarea nivelelor intermediarilor inflamatori are un impact semnificativ asupra proceselor aterosclerotice asociate cu inflamaţia.

Cuvinte cheie: *Parodontitele, inflamaţia, proteina C-reactivă*

INTRODUCTION

Lately there has been increasing evidence on the fact that patients suffering from periodontitis may present increased risk of cardiovascular disease. This risk appears to be independent of other known behavioral and medical risk factors, and, at the same time, it appears to be proportional to the severity of the periodontitis. Recent periodontology researches suggest that periodontitis predisposes to atherosclerotic coronary cardiovascular disease based on some local and derived systemic pro-inflammatory reactions similar to atherosclerosis and consisting of ***cytokines produced by monocytes*** and other inflammatory intermediaries induced by periodontal pathogens and their endotoxin, lipopolysaccharide. This mechanism may initiate vascular endothelial dysfunction with its effects on atherosclerosis and on the atheromatous plaque caused by the inflammation.(1) The inflammation is the physiopathological link between periodontitis – atherosclerosis – cardiovascular disease and everything connects obsessively starting from hygiene, meaning oral hygiene, chronic bacterial infection, gingivitis – periodontitis – local and systemic inflation. Several epidemiological studies on periodontal disease as risk factor for cardiovascular disease approached the premises according to which oral infection (periodontal) might disturb the levels of the systemic inflammatory intermediaries causing thus the mechanisms of atherosclerotic development.(2) This important development regarding the inflammation led to a concept alteration from "periodontal disease as oral problem of periodontitis – to the concept of impact factor on systemic health".(3) The fact that inflammation plays an important role in atherogenesis is a general accepted fact and the factors systemically amplifying the inflammation are continuously under study both clinically as well as from the point of view of fundamental research.

Cardiovascular systemic diseases are a major problem for public health as they impact on invalidity and mortality at national level, and medical concern is therefore necessary.

Scope of the study: to investigate the potential risk and the inflammatory link between the periodontal disease and the complications of the coronary cardiovascular disease.

Material and method: Starting from the premise that local periodontal infection might disturb the levels of the systemic inflammatory intermediaries and might promote the mechanisms of the coronary atherosclerosis – we compared the levels of the systemic inflammatory intermediaries at patients belonging to four study groups from the general trial group and we evaluated the clinical consequences.

From the extended group of 916 examined subjects we formed the following groups:

- group 1 – 86 patients diagnosed with chronic periodontitis in different clinical evolution stages with no other related pathology;
- group 2 – 67 patients diagnosed with coronary disease with various clinical forms (effort angina, unstable angina, ***sequelae*** of myocardial infarction with no other related pathology);
- group 3 – 59 patients diagnosed with chronic periodontitis and coronary disease with no other related pathology;
- group 4 – 50 volunteers with no clinically pathology - no pathological or imagistic biological pathology.

To evaluate the above mentioned diagnosis patients were subject to special clinical exams, biomoral and physical – imagistic exams. The groups were formed after the patients were informed on the purpose of our

action and after they agreed upon it, and it lasted for two years.

Demographic data

- ***Group # 1*** consisting of 86 patients diagnosed with chronic periodontitis,
  - divided by gender, as follows: 51 females (59,30 %),35 males (40,69 %)
  - divided by social background: urban 57 patients (66,27%), rural 29 patients (33,72%).

Average age of the group was 44 years, the youngest patient being 23 and the oldest 65.

Table no. 1. Group by age / gender

Age group	Patients Total	Females	Males
23-30	18 patients	15 (17.44%)	3 (3.48%)
31-40	17 patients	15 (17.44%)	2 (2.32%)
41-50	21 patients	5 (5.81%)	16 (18.60%)
51-60	19 patients	8 (9.30%)	11 (12.79%)
61-65	11 patients	8 (9.30%)	3 (3.48%)

- ***Group # 2*** consisting of 67 patients diagnosed with myocardial infarction and recently released form the hospital out of which:
  - By gender: 25 females (37.31%), 42 males (62.68 %)
  - By social background: 46 urban (68.65 %), 21 rural (31.34 %).

Average age of the group was 50.1, the youngest patient being 33 and the oldest 69.

Table no. 2. Group by age / gender

Age group	Patients Total	Females	Males
33-40	9	3 (4.47 %)	4 (5.97%)
41-50	14	5 (5.97%)	9 (13.43%)
51-60	26	8 (11.94%)	18 (26.86%)
61-69	18	9 (13.437%)	9 (13.00%)

- ***Group # 3*** consisting of 59 patients diagnosed with associated diagnosis of recent myocardial infarction and chronic periodontitis out of which:
  - By gender: 39 males (66.10%); 20 females (33.89 %)
  - By social background: urban 38 patients; rural 21 patients

Average age of the group was 49.5, the youngest patient being 33 and the oldest 66.

- ***Group # 4*** consisting of 50 volunteers – both periodonthologically and cardiologically clinically healthy.

The four study groups counted a number of 262 patients.

After the clinical and periodontitis exam performed at intervals during the two study years the following venous blood tests were performed for all patients:

- C-reactive protein;
- fibrinogen;
- immunizing electrical ionization alpha 2 ceruloplasmin;
- lipemic profile:
- total cholesterol;
- LDL – cholesterol;
- HDL – cholesterol;
- Triglycerides;
- preprandial glycemia.

The panoramic endo-oral x-rays for groups 1, 2 and 3 and their readings were performed by external specialty companies in Cluj and Timişoara; we got the written results. The normal values used for the biomoral tests were:

- C-reactive protein: < 0.8 mg / dl (185) ;
- fibrinogen: 2- 4 g/l (185);
- serum alpha 2 ceruloplasmin:22 – 63 mg/dl (185).

RESULTS

Table no. 3. The patients in the four study groups divided by the level of the analyzed inflammatory markers. C-reactive protein

C-reactive protein mg/l		No. of patients in each study group			
		Gr.1	Gr.2	Gr.3	Gr.4
< 0,8	Normal value	2 patients	7 patients	-	39 patients
1-3	Slightly increased value	2 3 patients	26 patients	4 Patients	8 patients
3-5	Moderately increased value	27 patients	16 patients	26 Patients	-
> 5	Highly increased value	34 patients	18 patients	29 Patients	3 patients

Table no. 4. The patients in the four study groups divided by the level of the analyzed inflammatory markers. Fibrinogen

Fibrinogen g/l	Group reference and no. of patients in each study group			
	1	2	3	4
	No. of patients in each study group			
< 2 – 4	24 patients	2 patients	9 patients	31 patients
4 – 10	26 patients	5 patients	15 patients	18 patients
10 – 15	17 patients	26 patients	19 patients	1 patient
>15	19 patients	34 patients	16 patients	-

Table no. 5. The patients in the four study groups divided by the level of the analyzed inflammatory markers. Alfa – 2 Ceruloplasmin

Alfa – 2 Ceruloplasmin	Group reference and no. of patients in the study group			
	1	2	3	4
	no. of patients in the study group			
22 - 63 mg/dl normal	38 patients	13 patients	30 patients	49 patients
63 - 100 mg/dl medium value	39 patients	32 patients	23 patients	1 patient
100 - 200 mg/dl increased value	9 patients	22 patients	6 patients	0

Table no. 6. Index of periodontal exam expressed by CPITN for the four study groups by no. of patients

CPITN	Group reference and no. of patients in the study group			
	1	2	3	4
0	0	6 patients	6 patients	50 patients
1	17 patients	14 patients	18 patients	0
2	19 patients	22 patients	12 patients	0
3	21 patients	11 patients	9 patients	0
4	29 patients	14 patients	11 patients	0

Assessing the data in the tables we conclude that the value of C-reactive protein is significantly higher at patients in groups 1 and 2, meaning the patients suffering from a periodontal or cardiovascular artery disease presenting values at least two times higher than those of group 4, the group that presents no affection whatsoever, and the subjects in group 3 that suffer from associated periodontitis and cardiovascular artery disease present 3 – 4 times higher values of C-reactive protein than those of the control subjects. Likewise, C-reactive protein is higher at patients presenting associated pathology than at patients with single pathology, whether periodontal or cardiovascular. Levels of fibrinogen were higher in the group presenting vascular pathology compared to group 1 and even group 3 that also present coronary disease. Likewise, ceruloplasmin was higher in group 2 with cardiovascular pathology presenting no reaction in the other pathological groups.

The alveolar bone loss and aspects of the carotid calcification, as signs of the evolution of atherosclerosis, were monitored by panoramic endo-oral x-rays.

Panoramic dental x-rays were performed at 30 patients in group 1, meaning the group diagnosed with chronic periodontitis, and at 20 patients in group 2, the group diagnosed with recent myocardial infarction. At group 1, after reading the panoramic dental x-rays, we found significant ***alveolar bone loss*** at 23 patients (76.66%) and carotid atherosclerotic plaques at 16 patients (53.33%), whereas at group 2, 20 of the panoramic dental x-rays evidenced major ***alveolar bone loss at 13 patients*** (65%) and carotid atherosclerotic plaques 17 patients (85%).

These dental x-ray exams (panoramic endo-oral) evidencing signs of *alveolar bone loss, vertical defects and the state of the molar bifurcation define the periodontal state and the identified signs of carotid calcification show the link between periodontitis and atherosclerotic vascular disease. The high percentage compared to the no. of performed x-rays* (no. of patients that went under x-ray exam) evidences a ratio of major alveolar bone loss of 76.66 %, as the main disease sign in different stages, and the percentage of 53.33 % for atherosclerotic plaques – evidences the high degree of association between the two affections. For group 2 the advanced atherosclerotic process associated with myocardial infarction was evidenced by 85% of the performed x-rays at this particular group showing atherosclerotic support through the presence of the atherosclerotic plaques and the association with periodontitis by signs of alveolar bone loss in 65 % of the performed exams showing thus, by this aspect as well, the association of atherosclerosis with periodontal disease.

Table no. 7. Presentation of biomarkers of lipid fractions by study groups and no. of patients in each study group

Lipid fraction in mg/dl (from blood serum)		No. of patients by diagnosis			
		1	2	3	4
Total cholesterol	<200mg/dl	45 patients	9 patients	19 patients	16 patients
	200-400 mg/l	41 patients	38 patients	21 patients	22 patients
	> 400 mg/dl	0	20 patients	19 patients	12 patients
LDL – C	<130mg/dl	57 patients	10 patients	13 patients	41 patients
	130-150 mg/l	22 patients	28 patients	33 patients	6 patients
	> 150 mg/dl	7 patients	29 patients	13 patients	3 patients
HDL - C	<35mg/dl	18 patients	34 patients	12 patients	0
	35-50 mg/l	48 patients	27 patients	36 patients	13 patients
	> 50 mg/dl	20 patients	6 patients	9 patients	37 patients
Triglycerides	<150mg/dl	27 patients	14 patients	16 patients	31 patients
	150-200 mg/l	31 patients	34 patients	28 patients	14 patients
	> 200 mg/dl	28 patients	11 patients	15 patients	5 patients

DISCUSSIONS

By monitoring the potential risk and the inflammatory connections between periodontitis and the complications of the cardiovascular coronary disease we may draw several conclusions based on the results of our investigations.

The inflammatory connections between the two affections are performed through common proinflammatory-markers such as C-reactive protein, various secretary cytokines at local inflammation as well as at systemic inflammation, atherosclerotic plaque or those clinically induced at the endoarterial epithelium.

It is important to note that the serum levels of C-reactive protein were higher in group 1 and 2 compared to group 4, both in the case of periodontitis as well as in the case of cardiovascular coronary disease, as sign of common marker, but in group 3 where periodontitis is associated with cardiovascular coronary disease complicated by myocardial infarction, due to the increase of the inflammation burden the level of C-reactive protein was transgressed. This is where the inflammatory process affects the destabilization of the atherosclerotic plaque.

A series of studies support the predictive value of C-reactive protein sampled from the patient suffering from coronary disease at admission and dynamic

monitoring during hospitalization correlated as maximum value at peak CK-MB enzyme and LDH level.

Patients committed for precordial pain but presenting no ECG or enzymatic changes presented infarction evolution towards myocardial infarction more frequently if they had levels of C-reactive protein higher than 3 mg/l (4). TIM II study showed that patients with levels of C-reactive protein higher than 15,5 mg/l presented a mortality risk of 5.8% at 2 weeks as compared to the patients with levels of C-reactive protein lower than 5,5 mg/l that presented a mortality risk of 0.36%. Increased levels of C-reactive protein after an acute coronary syndrome allow us to estimate the risk of a recurrent coronary event after 6 months (CAPTURE study).

C-reactive protein is a marker showing very dynamic changes in time and, therefore, its values expressed and considered as "diagnoses" – by various studies between 3 and 15 mg/ dl turn the comparison between them difficult.

From all the inflammatory markers studied for their potential role as risk factors C-reactive protein has the best laboratory test performance and presents the strongest association with cardiovascular events. Plasmatic C-reactive protein is produced by under the transcriptional control of pro-inflammatory cytokine (IL-6, IL-1, TNF alpha). The plasmatic level of C-reactive protein can be evidenced in 4 hours after tissue injury with 1000 fold increase in 24-27 hours.(4)

The serum level of C-reactive protein directly reflects the intensity of the pathological process that stimulated its production. C-reactive protein is also known as "the pro-inflammatory molecule" due to its ability to stimulate the activity of the complement in defense of the host and to mediate fagocitosis. C-reactive protein induces monocyte tissue factor production, a pro-coagulant playing a key role in arterial thrombosis.

The involving mechanisms of moderately increased levels of C-reactive protein in the evolution of the atherogene process or of the acute coronary events are not clear enough yet. But the inflammation is definitely involved in the evolution of the atherosclerotic plaque instability. This process occurs as a result of some stimuli produced by the acute phase reactants placed at the very level of the atheromatous plaque.

The increased attention paid in the last years to the connection between periodontitis and cardiovascular risk cleared up, to a great extent, the etiopathology of this association. Periodontitis is a chronic inflammatory infectious process. The infectious agent may act during the initial stages of the atherosclerotic process causing the evolution of the disease with all its characteristics.

CONCLUSIONS

1. The examination results of the four groups of patients support the mechanisms of the local and systemic pro-inflammatory reactions, derived from the host, similar to atherosclerosis, consisting of monocyte-derived cytokines and their endotoxins.
2. These mechanisms may be the start of the vascular endothelial dysfunction and cause ulterior sequela leading to atherosclerosis and complications of it.
3. Clinical evidence expressed through umoral markers shows the determination between the local inflammation and the systemic one as a result of the localized chronic infection.
4. The level change of the inflammatory intermediaries has a significant impact on the atherosclerotic processes associated with inflammation.(5)

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