Research Article

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ARCHIVES OF MEDICINE
ISSN 1989-5216

2017
Vol.9 No.1:3

DOI: 10.21767/1989-5216.1000186

The Association between the Condition of Dentition and Myocardial Infarction Risk

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Received date: December 26, 2017; **Accepted date:** January 10, 2017; **Published date:** January 17, 2017

Citation: Taraszkiewicz-Sulik K, Gabriela P, Maria G, Wlodzimierz M. The Association between the Condition of Dentition and Myocardial Infarction Risk. Arch Med. 2017, 9:1

Abstract

Introduction: Inflammatory process plays a great role in pathogenesis and development of many of the systemic diseases, including Cardiovascular Disease and Incident Cardiovascular Events (CVEs). Interleukin-6 and C-reactive protein are recognized as an inflammatory markers.

The Aim of the Study: To assess the level of the inflammatory markers: hs-CRP and IL-6, related to the number of remaining teeth in post-myocardial infarction patients, treated with primary coronary angioplasty (pPCI).

Materials and Methods: The research was based on 80 people, 32 women and 48 men aged 34-82. Within this sample of 80 people, 50 had previously suffered a heart attack while 30 were in good general health. The partially edentulous arches were classified with Galasińska-Landsbergerowa classification and the number of remaining teeth was assessed in both groups. The level of hs-CRP was measured with nephelometric method, IL-6 with immunoenzymatic method (ELISA). For statistical analysis the Statistica 10.0 software was used.

Results: In the post-myocardial infarction male group, the statistically significant negative correlation between IL-6 level and the mean remaining teeth in general, as well as in mandible was observed. However no correlation between the number of remaining teeth and CRP level, in post-myocardial patients, was noticed.

Conclusion: Increased level of hs-CRP and IL-6 in research confirms the hypothesis, that unsatisfactory oral hygiene status raises the risk of myocardial infarction. Hence, there is a necessity of creation and implementation of professional preventive-therapeutic-educational program dedicated directly to cardiac high risk group.

Keywords: Interleukin-6; C-reactive protein; Myocardial infarction

Introduction

The inflammatory process plays an important role in the pathogenesis and development of many of the systemic diseases, including cardiovascular disease and Incident Cardiovascular Events (CVEs). Over the years, the suggestions have appeared, that one of the inflammatory process factors is chronic infection [1-5]. It is highly possible, that inflammatory processes in periodontal tissues, may have an effect not only locally, in the oral cavity, but also generally in the human body [6-9].

Inflammatory markers

Understanding of the molecular basics of the inflammatory process, simplifies the identification of different markers which strategically may be used in anti-atherosclerosis treatment. The positive correlation between Acute Coronary Syndrome and inflammatory markers such as CRP, IL-1, IL-6, TNF-α was observed [10,11]. In blood plasma or serum it is possible to assess the concentration of inflammatory markers, such as Interleukin 6 (IL-6) and C-reactive protein (hs-CRP, high-sensitivity C-reactive protein). These markers are useful to identify people with high risk of Incident Cardiovascular Events [10-14]. Cytokines are the mediators of inflammatory process and immune response in human body. They are the key factors of periodontal pathologies. IL-6 is one of the multifunctional cytokines, it is the main element of inflammatory process cascade. There is a strong belief, that it is not only the biomarker of early, asymptomatic atherosclerosis but also the prognostication of Incident Cardiovascular Events. It is produced by various cells, such as osteoblasts, monocytes, fibroblasts, osteoclasts. IL-6, TNF-α and other cytokines take part in local and general anti-inflammatory response. During the periodontitis the concentrations of proinflammatory mediators significantly raises. Many studies confirmed the role of IL-6 in destructive processes of bone. It is one of the main mediators of acute-phase reaction, i.e. significantly stimulates inflammatory process and the synthesis of acute-phase proteins such as: C-reactive protein, amyloid A, beta-fibrinogen, alpha 1-antitrypsin,

haptoglobin, ceruloplasmin, complement component C3 and alpha 2-antitrypsin. It also provides feedback inhibition of TNF-α (Tumor Necrosis Factor alpha) synthesis. The IL-6 synthesis is stimulated in various cells, it may be also produced by neoplastic cell. From the inflammatory process the main source of IL-6 are: endothelium cells, fibroblasts, monocytes and macrophages. From among many of different properties of IL-6, the most important are the stimulation of lymphocyte B differentiation into plasma cells, activation (with IL-1) lymphocytes T, stimulation of hemopoiesis synergistically to IL-3, it is also pyrogenic factor (endogenous pyrogen causes fever). C-reactive protein (CRP) was described for the first time in 1930 by Tillett and Francis in Bacteriological Laboratory of Rockefeller Institute in New York. This protein was discovered during clinical studies under acute general inflammation in the body suffering from pneumococcal pneumonia [11]. CRP is the acute-phase protein, which does not change during the evolution of vertebrates, that suggests it's significant role in immune responses [15]. It is produced by liver, synthesized by hepatocytes and Borowicz-Kupffer cells to provide the modification and modulation of immune response to infection. The concentration in blood plasma raises dynamically, over hundred times during generalized inflammatory response. Main stimulants of the synthesis are cytokines, such as: IL-1, IL-6 and TNF-α. While phosphorylation of transcription factor IL-6, it activates the gene responsible for CRP synthesis. The characteristic feature of CRP is combining different calcium-dependent ligands as well as calcium-independent. The presence of calcium ions guarantees the combination of CRP with phosphocholine, which is the component of phospholipids arranged in the biological membrane or bacteria polysaccharides. The main biological function is the ability to opsonization of the superficial molecules of microorganisms and damaged human cells also to intermediate the elimination process by activation the complement system and phagocytes [16-21]. CRP is one of the most remarkable factor of acute-phase, and it's concentration in blood serum may increase several times. The growth is significantly higher in bacterial infections than in viral once, and the concentration of CRP is proportional to the level of tissue damage. The parameters cannot be interpreted without the clinical symptoms, because it is nonspecific factor [17-20]. The secretion of CRP starts in 4 h to 6 h after stimulation and reaches the highest level in next 36 h to 48 h. Biological half-time of CRP is about 19 h, it decreases up to 50% in one day after ended stimulation. According to normal concentration in serum CRP is in negligible and only a level above 10 mg/l to 15 mg/l can be assigned as a typical for acute-phase. Actual classification assigns CRP level for low (<1 mg/l), moderate (1 mg/l to 3 mg/l) and high (>3 mg/l) risk group. Increased level of CRP indicates two times higher risk of cerebral stroke or peripheral vascular disease, and three times higher risk of myocardial infarction. High-sensitivity testing methods helped to develop the methods to detect very low concentration of CRP (sensitivity 0.1 mg/l; hs-CRP-high sensitivity CRP), which allowed to detect very low-intensity inflammation. The CRP became a significant parameter because it is a nonspecific factor, to identify inflammatory process in population of externally healthy people but with high risk of Incident Cardiovascular Events, such as myocardial infarction, it is also very helpful in therapy planning [16,22,23].

The aim of the study

The assessment of the level of the inflammatory markers: hs-CRP and IL-6, related to the number of remaining teeth in patients after myocardial infarction, treated with primary angioplasty.

Material and Methods

The research was based on 80 people, 32 women and 48 men aged 34 years to 82 years, and the average age was 58 years old. The patients were divided into 2 groups:

Out of two groups, 1st Group contained 50 people, hospitalized in Department of Cardiology of Medical University of Białystok (Poland) for recent uncomplicated myocardial infarction, treated with primary angioplasty. The group contained 16 women and 34 men, aged 50 years to 82 years, and the average age was 64.4 years old.

The 2nd group is the control group included 30 people, generally healthy, who did not report any cardiovascular problems, and presented themselves at the Department of Prosthodontics of Medical University of Białystok (Poland) for check-ups. The group included 16 women and 14 men, aged 43 years to 75 years; the average age was 47.3 years.

The research was an implementation of own work on UMB, the testing protocol was in line with Helsinki Convention and was accepted by Bioethical Commission of Medical University of Białystok Nr RI-003/288/2005. The patients' consents were obtained, after informing them about the methods and aim of the study. Missing teeth in maxilla and mandible were noted in patient's charts. The partially edentulous arches was classified according to Galasinska-Landsbergerowa classification. The number of remaining teeth were written down in each patient's chart.

Laboratory Tests

The testing material was blood, drawed on empty stomach from basilic vein, about 6 ml, on Day 2 or 3 after incident cardiovascular events. Biochemical tests were performed in Department of Biochemical Diagnostics and Department of Allergology of Medical University of Białystok.

The assessment of IL-6 and hs-CRP concentration

The IL-6 level was measured in blood serum and it was detected with immunoenzymatic method (ELISA) (R&D brand's reagents). Acute-phase protein (hs-CRP) was measured with nephelometric method with the use of DADE-BEHRING Diagnostics brand's reagents. The results were presented as a mean numbers. For statistical analysis the Statistica 10.0 software was used.

Results

In research 80 people were examined, 32 women (40% of the population) and 48 men (60% of the population). In research group of 50 people with recent myocardial infarction (Group 1)

dominant are men (68%) comparing to women (32%). In control group (Group 2) of 30 people dominant was female population (53.3%), comparing to the male population (46.6%), the differences were close to statistically relevant (p=0.059) (**Table 1**).

Group	N	Sex			
		W		M	
		N	Percent (%)	N	Percent (%)
In total	80	32	40%	48	60%
Group 1	50	16	32%	34	68%
Group 2	30	16	53.3%	14	46,6%

Table 1 The percentage of women and men in subsequent groups.

The average age of all the patients was 58.0, the youngest patient-34 years old, and the oldest-82 years old. In research group the average age was 64.4 in age rate 50 years to 82 years old. In the control group-47.3 in age rate 34 years to 75 years old. The differences between groups were not statistically significant (p=24). The groups were compared according to the age (**Table 2**). The analysis of partially edentulous was presented in **Table 3**. Variables maxilla and mandible were represented in typical ordinal scale with five categories. Chi-square test (χ^2=20.4; df=4; p=0.00041; C=0.45) as well as Mann-Whitney U test (Z=4.03; p=0.0001) were statistically significant. In control group the variable was lower. The dentition was classified with the use of Galasinska-Landsbergerowa classification.

Table 2 Characteristics of the groups in relation to age.

Group	N	The average age (years)	Age range (years)
In total	80	58.0	34-82
Group 1	50	64.4	50-82
Group 2	30	47.3	34-75

Table 3 Missing teeth in subsequent groups.

G-L classification	Maxilla				Mandible			
	Group 1		Group 2		Group 1		Group 2	
Class	N	%	N	%	N	%	N	%
I	0	0.00%	5	16.70%	0	0.00%	5	16.70%
II	8	16.00%	11	36.70%	8	16.00%	14	47.70%
III	7	14.00%	7	23.30%	5	10.00%	4	13.30%
IV	16	32.00%	3	10.00%	25	50.00%	7	23.30%
V	19	38.00%	4	13.30%	12	24.00%	0	0.00%
In total	50	100.00%	30	100.00%	50	100.00%	30	100.00%

Group 1 χ^2=25.5; df=4; p=0,00004; C=0.43, test U Manna-Whitney Z=4.93; p=0.0000.
Group 2 χ^2=20.4; df=4; p=0.00041; C=0.45, test U Manna-Whitney Z=4.03; p=0.0001.

In the research group, in maxilla: the full edentulism was observed the most frequent (class V)-38%, and mixed teeth loss (class IV) i.e. uni-/bilateral edentulous area and unilateraledentulous area bounded anteriorly and posteriorly by remaining teeth-32%, uni-/bilateral edentulous areas (class III) was in 14% of research group, unilateral edentulous area bounded anteriorly and posteriorly by remaining teeth (class II) was observed in 16% of the patient. In control group the most frequent were unilateral edentulous area bounded anteriorly and posteriorly by remaining teeth (class II)-36,7%, class III -23,3%, class V-13,3% and full dentition-qualitative dental problems-class I-17,7% of patients, class IV-10%. Tests that have been used let us to reject the zero hypothesis (χ^2=25,5; df=4; p=0,00004; C=0,49 and Z=4,93; p=0,0000), which shows that in post-myocardial infarction patients in mandible the class IV was observed the most frequent-50% of the people. Class V-24%, class II-16% and class III-10% of the patient. In control group in mandible the class II was noticed the most frequent-46.7%, class IV-23.3%, class I-16.7, class III-13.3% (**Table 3**).

The analysis of the number of the remaining teeth, were presented in **Table 4**. In research group the average number of saved teeth was 10.2, in maxilla that number was significantly lower-4.32, in mandible slightly higher-5.88.

In control group the average number of saved teeth was relevantly higher-20.9, in maxilla-9.83, and in mandible 11.07.

The analysis of the number of remaining teeth in relation to sex in female research group showed, that the general number of saved teeth was lower-6.31; in maxilla 2.81, and in mandible 3.5. In male research group the average number of saved teeth was twice as high-12.03, in maxilla that number was lower-5.03, but in mandible was higher-7.0 (**Table 5**). In control group the average number of remaining teeth was approximate in female and male populations, 20.13 *vs.* 21.79. In female control group the number of remaining teeth in maxilla was lower-9.0 than in mandible-11.13. Although in male control group the number of saved teeth in maxilla and in mandible was approximate, 10.79 *vs.* 11.0 (**Table 6**). The concentration of interleukin-6 is

statistically significant in both groups (Z=6,65; p=0,0000). The comparisons of mean and medians shows that the higher IL-6 level had research group. The mean level in research group was 7.56 ± 3.24 pg/ml, while in control group the IL-6 level was 1.42 ± 1.00 pg/m (**Table 7**). The CRP concentrations were statistically relevant in both groups (Z=7.38; p=0,0000).

Table 4 The average number of remaining teeth in maxilla and manbible.

Variables	Group 1		Group 2	
	N	Mean	N	Mean
Teeth number: maxilla	50	4.32	30	9.83
Teeth number: mandible	50	5.88	30	11.07
Teeth number: in total	50	10.20	30	20.90

Table 5 The relation between the number of remaining teeth and sex in research group.

Variable	Women group 1		Men group 1	
	N	Mean	N	Mean
Teeth number: maxilla	16	2.81	34	5,03
Teeth number: mandible	16	3.50	34	7,0
Teeth number: in total	16	6.31	34	12,03

Table 6 The relation between the number of remaining teeth and sex in control group.

	Women group 2		Men group 2	
Zmienna	N	Mean	N	Mean
Teeth number: maxilla	16	9.00	14	10.79
Teeth number: mandible	16	11.13	14	11.0
Teeth number: in total	16	20.13	14	21.79

Table 7 The level of LI-6 in research group.

Group	Mean	Medians	Sv.	Z	P
Group 1	7.56	9.35	3.24	6.65	0.0000
Group 2	1.42	1.34	1.00		

Significantly higher levels were detected in research group: mean 63.02 mg/l ± 125.04 mg/l, comparing to control group: mean 1.28 mg/l ± 1.23 mg/l (**Table 8**). No significant correlation between the mean saved teeth number in maxilla and mandible, and IL-6 level in research group was noticed (**Table 9**).

In control group the statistically relevant (p=0.0159), negative correlation between teeth number in mandible and IL-6 level was observed (r=-0.44). While the mean number of teeth is raises up the IL-6 level is decreasing **(Table 10)**.

In the male research group, statistically relevant negative relations were noticed between the interleukin-6 level and the mean teeth number (p=0.0300, r=-0.37) but also between interleukin-6 level and the remaining teeth number in mandible (p=0.0261, r=-0.38**) (Table 11)**.

In control female group significant correlation was noticed between: the mean teeth number and IL-6 level (r=-0.55; p=0.0284) also between the average teeth number in mandible and IL-6 level (r=-0.64, p=0.0078). In both situations relevant, strong correlation is observed **(Table 12)**. The concentration of hs-CRP did not correlate with the mean teeth number in research as well as in control group, either in women and men populations **(Tables 13 and 14)**.

Table 8 The level of hs-CRP in subsequent groups.

Group	Mean	Medians	Sv.	Z	P
Group 1	63.02	20.63	125.04	7.38	0.0000
Group 2	1.28	0.96	1.23		

Table 9 The level of IL-6 and a number of remaining teeth-research group.

Group 1			
Variables	N	R Spearman	P
Teeth number: maxilla and interleukin 6 (pg/ml)	50	-0.10	0.4955
Teeth number: mandible and interleukin 6 (pg/ml)	50	-0.13	0.3654
Teeth number: in total and interleukin 6 (pg/ml)	50	-0.14	0.3451

Table 10 The level of IL-6 and a number of remaining teeth-control group.

Group 2			
Variable	N	R Spearman	P

Teeth number: maxilla and interleukin 6 (pg/ml)	30	-0.21	0.2580
Teeth number: mandible and interleukin 6 (pg/ml)	30	-0.44	0.0159
Teeth number: in total and interleukin 6 (pg/ml)	30	-0.33	0.0725

Table 11 The level of il-6 and the number of remaining teeth in relation to sex- research group.

	Group 1 women			Group 1 men		
Variable	**N**	**R**	**P**	**N**	**R**	**P**
Teeth number: maxilla and IL6 (pg/ml)	16	0.19	0.4780	34	-0.29	0.1012
Teeth number: mandible and IL6 (pg/ml)	16	0.30	0.2619	34	-0.38	0.0261
Teeth number: in total and IL6 (pg/ml)	16	0.30	0.2664	34	-0.37	0.0300

Table 12 The Level of Il-6 and the number of remaining teeth in relation to sex- control group.

Variable	**Group 2 women**			**Group 2 men**		
	N	**R**	**P**	**N**	**R**	**P**
Teeth number: maxilla and IL6 (pg/ml)	16	-0.45	0.0781	14	0.41	0.1401
Teeth number: mandible and IL6 (pg/ml)	16	-0.64	0.0078	14	0.08	0.7762
Teeth number: in total and IL6 (pg/ml)	16	-0.55	0.2664	14	0.34	0.2284

Table 13 The level of hs-CRP and the number of remaining teeth in relation to sex- research group.

Variable	**Group 1 women**			**Group 1 men**		
	N	**R**	**P**	**N**	**R**	**P**
Teeth number: maxilla and crp (mg/l)	16	-0.08	0.7685	34	0.02	0.9325
Teeth number: mandible and crp (mg/l)	16	-0.09	0.7290	34	0.04	0.8432
Teeth number: in total and crp (mg/l)	16	-0.10	0.7258	34	0.01	0.9602

Table 14 The level of hs-CRP and the number of remaining teeth in relation to sex-control group.

Variable	**Group 2 women**			**Group 2 men**		
	N	**R**	**P**	**N**	**R**	**P**
Teeth number: maxilla and crp (mg/l)	16	-0.05	0.8677	14	0.05	0.8664
Teeth number: mandible and crp (mg/l)	16	-0.20	0.4609	14	-0.10	0.7296
Teeth number: in total and crp (mg/l)	16	-0.12	0.6675	14	-0.04	0.8867

Discussion

The usual assessment index, of the oral cavity health, is its dentition status. Desvarieux and others state that the tooth loss is the marker of periodontal disease in the future and the higher risk of atheromatous plaque [24-26].

In the research group, significant dentition problems were observed. In 38% of the patient in maxilla the edentulism was noticed, and 32% of the patient had extensive mixed teeth loss. In mandible the situation seemed to be slightly better, edentulism-24%, and mixed teeth loss-50% of the patients. The average number of remaining teeth was 10.2, in maxilla-4.32, and in mandible-5.88. The better situation was in control group, because the mean saved teeth number was 20.9, in maxilla 9.83, and in mandible 11.07. The differences in remaining teeth number between research and control group were statistically significant.

From anamnesis of the research group, it was determinate that the tooth loss was caused by untreated dental caries and periodontal diseases, patients did not want to treat their teeth but have chosen to extract them instead.

In Berent and other's research [27] in 349 of the patients suffering from cardiovascular disease and in 117 of the patients without cardiovascular problems the mean saved teeth number was approximately 15 ± 10 teeth, the differences between the groups were not statistically relevant. The edentulism was observed in 15.1% of the cardiovascular disease's patients and 14.88% of the patients from control group. In research group the number of edentulous patients was higher: the maxilla edentulism had 38% of the population and mandible 24% of the population. In control group the maxilla edentulism was observed in 13.3% of the patients.

Ziebolz et al. [28] in his research in Goettingen University of 33 patients: 17-post-myocardial infarction and 16-with angina pectoris, aged 34 years to 68 years old, had 8.4 ± 5.2 lost teeth and it was higher comparing to the control group-5.8 ± 6.6 lost teeth, the differences were not statistically relevant.

Own research-in the group of post-myocardial infarction patients of similar age, the number of lost teeth was higher. The control group included slightly younger people, that is why the tooth loss was compared to other author's studies.

Finnish authors Paunio et al. [29] tried to find a connection between the chronic dentogenic infection, characterized as the number of lost teeth and cardiovascular disease. They showed that the frequency of cardiovascular disease presence in research group with less than sixteen missing teeth, was 10% and raises two times in those patients who lost more than sixteen teeth. The number of lost teeth seemed to be statistically significant factor of the risk of cardiovascular disease, but only in smokers. In Li et al. [30] research of 103 people after myocardial infarction aged 68 ± 41-84 years old, the teeth loss number was lower, the average number of missing teeth was 6.89 ± 7.39. In control group of 52 people, the mean number was 4.21 ± 5.62, the differences were statistically relevant. However Elter [31] observed increased risk of cardiovascular disease in patients with significant edentulous area and high Clinical Attachment Level parameters. Holmlund [32] showed relevant correlation between the myocardial infarction and the average number of missing teeth in group of 3352 people, who required periodontal treatment and presented themselves with that problem at the dental office. Also Desvarieux [24] and other authors stated the positive correlation between the number of lost teeth and the frequency of atheromatous plaque presence in cervical arteries, detected in ultrasound [25,31].

In own research, in post-myocardial infarction patients, the average number of remaining teeth was lower compared to the control group.

Summary

- Elevated hs-CRP and IL-6 levels in research group, confirms the influence of unsatisfactory oral hygiene on higher risk of myocardial infarction.
- Represented results showed the necessity of creation and implementation professional preventive-therapeutic-educational program dedicated directly to cardiac patients.

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