Case Report

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Correlation of the cytokine status, arterial stiffness and oral health status in patients with the metabolic syndrome

Keywords: periodontitis, inflammation, cytokine, IL–10, IL–4, IL-1β, IL–8, IL–6, TNF–α, periodontal index, periodontitis, arterial stiffness, hyperglycemia, hypertension

Abbreviations: GP, general periodontitis; CVD, cardiovascular diseases; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins

Introduction

The present article provides data on the reliable relationship between the intensity of periodontal tissue affection and the increase in arterial stiffness in patients having hyperglycemia, an increase in the waist circumference and severe arterial hypertension. The cytokine status tends to change, thus leading to an increase in inflammation in the periodontal tissues.

Dental health is an important component of somatic human health. Various aggressive environmental and nutritional factors affect adversely the oral cavity homeostasis, serve as a prerequisite for emergence of inflammatory-destructive diseases of the dentofacial system. Development of general periodontitis (GP) is accompanied by a complex of pathological changes with a predominance of inflammatory and dystrophic phenomena.[1] These changes vary much, depending on the intensity of the periodontal tissue affection, and reflect the processes of local inflammation and activation of the immune defense mechanisms. All this requires adequate measures to control dental health of the population.[2] Diseases of periodontal tissues remain one of the urgent problems in the modern dentistry.[3] In recent decades, a large number of studies have been devoted to the relationship between the intensity of the periodontal complex affection and a number of somatic diseases, which are currently classified as socially significant ones. These are, first of all, cardiovascular diseases (CVD), diabetes mellitus, oncopathology, osteoporosis, osteoarthrosis, etc.[2,4–7] In the industrialized countries the prevalence of metabolic syndrome among the population of 30years and older is 10-20%, significantly increasing with age.

Goal of the study

identifying the correlation of the cytokine status, arterial stiffness and oral health status in patients with the metabolic syndrome.

Materials and methods of the study

The study included 100 male patients of 48 to 58years of age (the mean age was 53.1±8.2years) with chronic general periodontitis of different severity: 1 group - mild severity (29 persons), 2 group - moderate severity (38 persons), 3 group - heavy severity (33 persons), who had at least 20 teeth in their oral cavity and suffered from the metabolic syndrome; the control group consisted of 90 men, with chronic general periodontitis, but who did not have the metabolic syndrome in their anamnesis.

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At the time of enrollment, the patients had non-sanitized oral cavity. All 100 patients had 3 or more risk factors for CVD and suffered from general periodontitis. General Periodontitis was diagnosed on the basis of clinical (CPI (complex periodontal index), PMA (papillary marginal alveolar index), MBI (Muhlemann bleeding index) and radiographic data. The diagnosis was verified according to the WHO classification (1999). Criteria for the study subjects' discontinuation were applied to those patients having secondary forms of arterial hypertension, who had myocardial infarction or an episode of unstable angina in their anamnesis less than 6 months prior to enrollment, having hepatic or renal failure, oncological diseases and inflammatory diseases of a different genesis. Also women whose endocrine changes could be related to age were also excluded from the study. Collection of clinical material was carried out at the National Center of Cardiology and Therapy named after M.M. Mirrakhimov, polyclinic of the NCCT and clinics of the Department of Surgical Dentistry of the KRSU. The patients addressed independently or were referred by other medical specialists because of intensive signs of periodontitis.

The following methods were used to study the patients:

i. To diagnose pathologies of periodontal tissues, the complex periodontal index (CPI) was determined.

ii. To assess the severity of gingivitis (and subsequently record the dynamics of the process), the papillary marginal alveolar index (PMA) was used.

iii. To assess bleeding gums, Muhlemann bleeding index was used in the Cowell modification.

iv. Panoramic radiography was used for detailed examination of certain denture areas, in order to establish diagnosis of the oral cavity more accurately.

v. Determination of the status of the TNF-α mass and interleukin-10.

vi. Determination of the tumour necrosis factor alpha (TNF-α) mass and interleukin-10 (IL-10) was carried out by the method of solid-phase enzyme-linked immunosorbent assay with use of

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specialized test systems of CITOKIN-STIMUL-BEST company, Novosibirsk (Russia).

vii. To detect metabolic syndrome, we performed blood sugar tests and calculated the body mass index of the patients.

viii. Measuring of the blood pressure (according to Korotkov's method) was carried out on both hands with use of an aneroid sphygmomanometer. Measuring of the blood pressure was made with adherence to generally accepted rules (WHO, 1986).

ix. Biochemical blood tests were performed to determine the level of fatty acids and fibrinogen. To assess the lipid metabolism, a lipidogram (total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL)) was examined. The content of sugar, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL) was determined on a biochemical auto-analyzer Sinhron CX4-DELTA from Beckman, USA.

Results of the study

In the first group with a mild severity (29 persons), the outcomes of clinical studies revealed the following: CPI 1.6-2.7 points; PMA 25-33%, Muhlemann index 0.7-1.0 (29 persons), resorption of the interalveolar septa to 1/4 of the tooth root length was determined radiologically, as well as the compact plate absence on the alveolus apex and adjacent side sections. In the second group of patients with signs of moderate severity of inflammation (38 persons), the outcomes of clinical studies revealed the following: CPI 2.8-3.5 points, PMA 46-51%, Muhlemann index 1.4-2.5, and in the patients of 52-55years old, the roentgenogram distinctly showed resorption of the alveolar bone to 1/2 of the tooth root length, this resorption resulted in a vertical, horizontal and mixed type of atrophy; there is an increase of the spongy bone looping. The third group with severe periodontitis consisted of the patients older than 56years (33 persons) and showed CPI of 4.2-4.6 points and higher, PMA 57-60.5, Muhlemann index 2.6-2.9, and the roentgenogram revealed resorption of the alveoli by 3/4 of the tooth root length and more (Table 1).

When analyzing the hemodynamic and metabolic parameters, the following results were obtained. It turned out that the patients of the first and second groups were comparable with each other in respect of the severity of lipid, fat and carbohydrate metabolism violations ($p<0.05$) (Table 2).

Qualitatively different data were obtained in the patients with severe course of chronic general periodontitis. Thus, the blood sugar level in the first group patients, being equal to 4.2±1.0mmol/L, was significantly less than in the patients of the second and third groups (5.9±1.3mmol/L and 7.2±2.1mmol/L, P1-2<0.05 and P1-3<0.05), and in the patients of the 3rd group the hyperglycemia was significantly higher and in comparison with the patients of the second group (P2-3<0.05). In addition, the patients of the 3rd group with severe GP showed the highest serum fibrinogen levels (4,615±765mg/L in the third group compared to 4,038±839mg/L in the first group and 4,215±1,015 in the second group, $p<0.05$). Similar data were obtained with respect to the waist measurement: the value of this index in the first group was equal to 97.1±9.0cm and was significantly less than in the second and third group (104.1±5.1cm and 109.3±9.0cm, P1-2<0.05 и P1-3<0.05). The waist measurement of the patients of the third group was significantly higher and compared to the patients of the second group (P2-3<0.05).

Table 1 Dental indices in the patients with GP against the background of the metabolic syndrome (MS)

Degree of GP severity dental indices	Light (n=29)	Average (n=38)	Heavy (n=33)	Group as a whole(n=100)
Hygienic index	1,55±0,30	3,11±0,35	4,06±0,50	2,85±0,30
CPI	1,6±0,3	2,8±0,5	4,2±0,4	2,7±0,4
PMA	28±4,8	46±5,1	57±3,5	42,3±3,7
Muhlemann index	0,7±0,2	1,4±0,3	2,6±0,3	1,6±0,28

Taking into consideration the data provided in Table 2 concerning the correlation of the MS and KPI indices, it was naturally expected that the latter correlated with the levels of systolic (SBP) and diastolic (DBP) blood pressure. In the first group, the SBP and DBP levels were 142±17mm Hg and 92±6mm Hg, respectively, which were significantly less than in the patients of the second and third groups (157±19mm Hg, 98±8mm Hg and 162±16mm Hg, 106±11mm Hg, respectively, P1-2<0.05и P1-3<0.05), and in the patients of the third group the severity of arterial hypertension was significantly higher than in the patients of the second group (P2-3<0.05).

There were no significant differences between the patients having general periodontitis of various severity ($p<0.05$) in respect of the rest of biochemical indices of the metabolic syndrome (Table 2).

In the inflamed periodontal tissue, the level of inflammatory mediators associated with the process of tissue destruction, such as TNF-α, IL-6, prostaglandin E2 and matrix metalloproteinases,[8] usually increases. TNF-α is considered as the main mediator that determines emergence and progression of inflammation in the periodontal tissues. An increase in its content in the oral and gingival fluids or in the periodontal tissues due to inflammation has been proved by many researchers.[8–10] Next, we analyzed the content of pro- and anti-inflammatory cytokines in the patients with GP of various severity (Table 3).

As it follows from the data provided, TNF-α levels demonstrated a clear tendency to increase as the pathological process progressed. Thus, in patients with the GP of mild severity, the concentration of TNF-α was 6.57±0.72ng/ml, which was significantly lower in comparison with patients of the second group (7.62±0.43ng/ml, $p<0.001$). In patients with severe GP, the highest serum TNF-α level (9.15±1.06ng/ml) was recorded, which was significantly higher in comparison with the patients of the first and second groups ($p<0.001$). Most researchers consider TNF-α to be one of the main interleukins involved in the pathogenesis of the periodontal tissue diseases.

Moreover, we should note that the high level of TNF-α in case of severe GP does not only support the periodontal tissue inflammation, but also activates production of metalloproteinases, promotes destruction of collagen and resorption of the bones. Dynamics in IL-10 concentration were somewhat different as the pathological process progressed.[9,11] The anti-inflammatory cytokine interleukin-10 (IL-10) can inhibit production of TNF-α and weaken its negative effects.[10,12,13] As it can be seen from the data provided in Table 3, the level of this cytokine was similar in the patients with GP of the first and second groups (p<0.05). At the same time, with a severe course of the disease, the concentration of IL-10, amounting to 10.7±1.32pg/ml, was significantly higher than the values of similar parameters in the patients with GP of mild and moderate severity (p<0.005). It is known that IL-10 is one of the main anti-inflammatory cytokines and the most sensitive markers of systemic and local inflammation. Intense secretion of pro-inflammatory cytokines (TNF-α, IL-6, IL-1), IL-10 thereby limits excessive immune shift. Detection of an increase in IL-10 concentration levels in case of the severe disease seems to be regarded as a compensatory and adaptive mechanism that limits the inflammatory response and prevents progression of the disease. Analysis of the dynamics in the ratio of pro-/anti-inflammatory cytokines showed the following. The value of TNF-α/IL-10 ratio in the patients with a mild severity of GP was equal to 0.69±0.17units, while in the patients of the second group, the value of TNF-α/IL-10 ratio was significantly higher (0.81±0.12units, p<0,001), thus indicating a shift in the balance between pro-/anti-inflammatory cytokines in the medium-to-moderate severity of the disease towards predominance of the former with an increase in inflammatory changes in the periodontium. At the same time, in the patients with severe GP, the value of TNF-α/IL-10 ratio did not significantly change in comparison with the patients of the second group and was equal to 0.86±0.14units (p<0.05) compared to the second group, which again indicates the increasing role of IL-10 in limiting inflammation in case of general periodontitis of heavy severity.When analyzing the arterial stiffness parameters in patients with GP against the background of the metabolic syndrome, the following results were obtained (Table 4).

Table 2 Metabolic indices in the patients with GP against the background of the metabolic syndrome (MS)

Indicators	1 Group(n=29)	2 Group (n=38)	3 Group (n=33)	P
Age	52,1±4,2	50,9±3,8	51,8±4,8	нз
Level of sugar	4,20±1,02	5,9±1,3	7,21±2,18	P1-3-нз
				P2-3<0,025
Waist	97,1±9,0	104,1±5,1	109,3±9,0	P1-3<0,05
				P2-3<0,01
Body Mass Index	29,8±3,4	30,1±4,2	33,1±2,8	P1-3<0,05
				P2-3<0,01
				P1-3<0,05
Systolic blood pressure	142±17	157±19	162±16	P2-3<0,01
Diastolic blood pressure	92±6	98±8	106±11	нз
OXS	5,14±1,05	5,09±0,85	5,16±1,16	нз
LDL	2,89±1,13	3,14±0,86	3,26±1,25	нз
HDL	0,81±0,21	0,79±0,16	0,85±0,13	нз
TG	2,21±1,41	2,43±1,12	2,44±0,89	нз
Fibrinogen	4039±839	4215±1015	4615±765	P1-3<0,05 P2-3-нз

Table 3 Correlation of TNF-α and IL-10 with the GP intensity

Indicators	I (n=34)	II (n=26)	III (n=38)	p
TNF-α	6,57±0,72	7,62±0,43	9,15±1,06	нз
IL-10	9,47±1,39	9,43±1,28	10,7±1,32	нз
TNF-α / IL-10	0,69±0,17	0,81±0,1	0,86±0,14	нз

It was found that the augmentation index, normalized to the heart rate of 75 beats/min (Aix75), in the patients of the first and second groups (9.2±10.2% and 9.2±11.7%, p<0,005) was significantly lower than in the patients in the third group (16.6±10.7). Similarly, the Aix index in the patients of the first and second groups (9.0±10.2% and 11.1±13.7%, p<0.01) was significantly lower than in the patients of the third group (20.9±13.3%). In respect of the stiffness index (SI) and augmentation (RI), no significant changes were found between the three groups of patients (p>0.05).

Table 4 Arterial stiffness indices in the patients with general periodontitis against the background of the metabolic syndrome

Indicators	1 group (n=34)	2 group (n=26)	3 group (n=38)	P1-2<	P1-3<	P2-3<
Age	49,1±3,1	52,0±2,8	56,1±4,2			
Aix 75, %	9,0±10,2	9,2±11,7	16,6±10,7	0,005	0,005	НД
Aix, %	10,9±10,5	11,1±13,7	20,9±13,3	0,01	0,01	НД
Spa, мм рт.ст.	136±17	137±19	145±22	НД	НД	НД
SI, м/с	7,4±1,1	7,5±1,3	7,5±1,2	НД	НД	НД
RI, %	9,0±10,2	9,2±11,7	16,6±10,7	НД	НД	НД

Note: N/A - differences between the groups are not accurate.

When analyzing the study results obtained, we found out a close relationship between the severity of the periodontal tissue affection and arterial stiffness in the patients with general periodontitis, particularly, with the Aix 75 and Aix parameters.

Conclusion

Analysis of the obtained data concerning correlation of the periodontal tissue affection intensity and the metabolic syndrome components showed the following: parameters of changes in the lipid analysis and the BMI have no effect on general periodontitis against the background of the metabolic syndrome. Also, the values of arterial stiffness, blood sugar level, waist measurement and arterial hypertension affect directly the severity of general periodontitis, manifested in the aggravation of the clinical course of GP. Immunological indicators at the beginning of the chronic process (IL-10) remain stable. At the same time, TNF-α increases, resulting in a shift in the balance between IL-10 (anti-inflammatory cytokine) and TNF-α (pro-inflammatory cytokine), thus leading to an increase in inflammation in the periodontium. This, in turn, activates enzymes (metalloproteinase), which promote destruction of collagen and bone resorption. When general periodontitis turns to a severe form, IL-10 increases, which, in our opinion, is a compensatory mechanism aimed at limiting the excessive inflammatory response. Thus, in the complex pathogenesis of GP, we proved the effect of not only known factors, but also revealed the same of such indices as arterial stiffness, cytokine status, was revealed. Some researchers[14] suggested that improvement of the periodontal condition would positively affect metabolic control, while in other studies this positive effect was not evaluated.[15] Solidarity of universal pathogenetic mechanisms of inflammatory periodontal affection development, especially in patients with the metabolic syndrome, requires a complex, dynamic assessment of cytokine metabolism in this group of patients.

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None.

Conflicts of interest

The author declares no conflicts of interest.

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