ORIGINAL ARTICLE

Age Peculiarities of the Pro-inflammatory Component of Cytokine Profile in Chronic Odontogenic Infection Affected by Polymorbid Pathology

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Abstract

Aim: This study aimed to study the features of pro-inflammatory component of the cytokine profile in chronic odontogenic infection affected by polymorbid pathology. **Materials and Methods:** The study included 251 people: 125 middle-aged people (40–49 years) and 126 elderly people (60–69 years). All the people included in the study were divided into groups: Group 1 - apparently healthy people (33 patients of middle age and 31 of elderly age); Group 2 - patients suffering from chronic apical periodontitis (CAP) in granulating form (31 middle-aged patients and 33 elderly age patients); Group 3 - patients with CAP and coronary heart disease (CHD) (30 patients of middle age and 32 of elderly age); and Group 4 - patients suffering from CAP, CHD, and type 2 diabetes (31 middle-aged patients and 33 elderly patients). In all patients of different ages, cytokine profile was studied in blood serum, oral fluid, and crevicular gingival fluid. **Results:** The level of tumor necrosis factor alpha (TNF-α) in the blood serum depends significantly on the presence of a combination of CAP and CHD, CAP, CHD, and type 2 diabetes. A significant increase in the level of TNF-α in the oral and gingival fluids was noted when associated with polymorbid background in people of both the age groups. In the isolated course of CAP in elderly patients, unlike middle-aged patients, there was a significant increase in the concentration of interleukin (IL)-1β in blood serum. The level of IL-6 in the oral and gingival fluids is indicative of the characteristics of the inflammatory immune response in patients with CAP. The serum levels of IL-8 in elderly people are significantly higher than in middle-aged people. The increase in polymorphism leads to a significant increase in the degree of IL main in terms of IL-8. **Conclusion:** Concentration of TNF-α in blood serum with CAP can serve as an integral measure of immune inflammation. The level of IL-1β in blood serum, oral fluid, and gingival fluid can be considered as an additional factor characterizing the pathological process in polymorbid pathology. The level of IL-6 in the oral and gingival fluids is indicative of the characteristics of inflammatory immune response in patients with CAP. The severity of proinflammatory reaction by concentration of IL-8 is age dependent with a tendency of significant increase in the transition from middle to elderly age.

Key words: Chronic periodontal disease, odontogenic infection, polymorbid pathology, pro-inflammatory cytokines

INTRODUCTION

Prolonged progressive course of oral cavity diseases contributes to the formation of chronic odontogenic foci of infection, which are a source of sensitization and reduction of the level of non-specific resistance of the body.[1,2] Along with this, one of the most important features for people of older age groups is the simultaneous progression of more than two or three diseases,

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with the mutual influence, of which the classical clinic of the pathological process changes, the nature of its course, the number of complications increases, and the quality of life deteriorates.[3-5]

Suppression of non-specific resistance of the body is a risk factor for exacerbation of not only chronic general disease but also forms a lesion of hard tooth tissue, which in turn leads to progression of the pathological process not only of the dentofacial system but also other body systems (cardiovascular, immunological, etc.).[4-10]

The aim of the study

The aim is to study the features of the pro-inflammatory component of the cytokine profile in chronic odontogenic infection affected by polymorbid pathology.

MATERIALS AND METHODS

The study included 251 people: 125 middle-aged people (40–49 years) and 126 elderly people (60–69 years). All the people included in the study were divided into several groups [Table 1].

All patients of the Group 3 suffered from chronic apical periodontitis (CAP) in granulating form, coronary heart disease (CHD) in the form of I-III functional class (FC) effort angina, and I-II FC chronic heart failure (CHF) according to the New York Heart Association (NYHA) classification. All patients in the Group 4 suffered from CAP in the granulating form, CHD in the form of angina pectoris I-III FC, CHF IK II-II according to the NYHA classification, and type II diabetes.

In all patients of different ages, cytokine profile was studied in patients with CAP, a combination of CAP and CHD, CAP, IHD, and diabetes. The content of tumor necrosis factor alpha (TNF-α), interleukins (IL)-1β, IL-6, and IL-8 was studied in blood serum, oral fluid, and gingival fluid.

The level of cytokines (TNF-α, IL-1β, IL-6, and IL-8) was determined by the enzyme-linked immunosorbent assay using reagents from ZAO Vector-Best, Novosibirsk, using Thermo Scientific Multiskan GO tablet spectrophotometer.

Statistical method

Statistical processing of the material was performed on a personal computer in statistical software packages, Microsoft Excel, Statistical 6.0. During the statistical analysis of the material, intensive and extensive indices of mean values were calculated, and the reliability of differences in the mean and relative values determined by the Student's *t*-test was determined.

RESULTS AND DISCUSSION

Concentration of TNF-α in blood serum, oral fluid, and gingival fluid

The increase of TNF-α in blood serum is one of the most prominent signs of developing immune inflammation. We found that the level of TNF-α in blood serum is significantly affected by the presence of a combination of CAP and CHD, CAP, CHF, and concomitant type 2 diabetes.

The level of TNF-α in the oral fluid is not significantly different from that in apparently healthy people of middle and elder age, $P > 0.05$. A significant increase in the level of TNF-α in the oral fluid was noted in patients of middle and elderly age with CAP. The addition of CHD and type 2 diabetes significantly increased the TNF-α content in the oral fluid in people of both age groups, and these changes were more pronounced in elderly people ($P < 0.05$).

The level of TNF-α in the gingival fluid in the presence of CAP as monopathology significantly increases ($P < 0.05$) by approximately 4 times in people, of both middle and elderly age, and continues to progressively increase as the degree of polymorbidity increases.

Data are represented in Table 2 and Figure 1.

Thus, for a healthy person, both in the middle and elderly ages, a certain elevated level of TNF-α concentration is characteristic, as a reflection of the pro-inflammatory response of the immune system to various mediators of exogenous and endogenous origin. In this case, the concentration of cytokine in blood serum is an integral indicator of immune inflammation, and concentrations in the oral and gingival

Table 1: Characteristics of patients included in the study (abs.)

Groups of patients	Middle age	Elderly age	Total
Apparently healthy people	33	31	64
Patients suffering from chronic apical periodontitis in a granulating form	31	30	61
Patients suffering from chronic apical periodontitis and chronic heart decease	30	32	62
Patients suffering from chronic apical periodontitis, CHF, and type 2 diabetes	31	33	64
Total	125	126	251

CHF: Chronic heart failure

Table 2: TNF-α content in blood serum, oral cavity, and gingival fluid, pg/ml

Studied indicator	Age	Level of signal molecules			
		Healthy	CAP	CAP+CHD	CAP+CHD+type 2 diabetes
TNF-α in blood serum	Middle	68.2±3.4	71.0±3.5	92.8±3.8*,#	98.2±3.9*,#
	Elderly	69.0±3.2	73.0±3.5	111.1±4.4*,#,○	120.8±4.5*,#,○
TNF-α in oral cavity	Middle	12.8±1.1	22.0±2.0	27.1±2.1*,#	35.2±2.4*,#
	Elderly	15.0±1.2	2.1±2.2	34.3±2.3*,#,○	41.1±2.5*,#,○
TNF-α in gingival fluid	Middle	3.4±0.3	12.0±1.0	15.0±1.2*,#	19.9±1.9*,#
	Elderly	3.7±0.4	17.1±1.5	20.1±1.9*,#,○	25.4±2.2*,#,○

*P<0.05 compared to healthy people, #P<0.05 compared to patients with CAP, ○P<0.05 compared to middle-aged patients. CAP: Chronic apical periodontitis, CHD: Coronary heart disease, TNF-α: Tumor necrosis factor alpha

fluid are only mediated by a fragmentary index of the general status of the neuroimmune system of the body.

In case of CAP, the resorption of the bone tissue of the tooth is confirmed by X-ray and is one of the characteristic signs of the disease. Obviously, a significant increase in the concentration of TNF-α in patients with CAP activates osteoclasts and indirectly enhances resorptive processes. The situation is significantly complicated with an increase in the degree of polymorbidity: When associated with CHD and type 2 diabetes, the level of TNF-α increases even more [Figure 1], which further enhances the resorptive processes in the bone tissue of the tooth root.

Inflammatory process in the area of CAP becomes more generalized and captures adjacent tissues. Therefore, an obvious practical conclusion from our experimental data is the necessity to actively reduce the expression of TNF-α in patients with CAP, especially when accompanied by CHD and type 2 diabetes.

The concentration of IL-1α in blood serum, oral fluid, and gingival fluid

In the isolated course of CAP in elderly patients, unlike middle-aged patients, there was a significant increase in the concentration of IL-1β in blood serum. A further increase in polymorbidity led to a significant ($P < 0.05$) increase in the degree of interleukemia in terms of IL-1β in both the groups of patients.

The dependence of the IL-1β content in the oral fluid on the age of patients and the degree of polymorbidity practically repeats that for serum IL-1β but with lower absolute indices.

The nature of the dependence of the IL-1β content in the gingival fluid on the age of patients and the degree of polymorbidity is different from that for IL-1β in blood serum and oral fluid. In the isolated course of CAP, there was a significant ($P < 0.05$) increase in the content of this signal molecule in the gingival fluid. A further increase in polymorbidity led to a significant ($P < 0.05$) increase in the degree of interleukinemia in terms of IL-1β. At the same time,

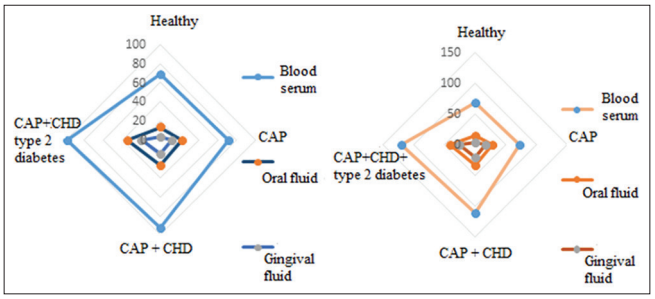

Figure 1: The concentration of tumor necrosis factor alpha in different biological samples in middle-aged (a) and elderly people, (b) with different degree of polymorbidity (pg/ml)

significant differences in comparison with the middle age were observed only in patients with CAP + CHD ($P < 0.05$) [Table 3 and Figure 2].

As shown in Figure 2, the level of IL-1β in blood serum, oral fluid, and gingival fluid can be considered as an additional factor characterizing the pathological process in polymorbid pathology including CAP: CAP + CHD and CAP + CHD + type 2 diabetes. However, in case of isolated course of CAP, significant differences between the level of IL-1β ($P < 0.05$) in patients and apparently healthy people are found only in the gingival fluid, which is likely due to the peculiarities of localization of IL-1β-expressing cells in CAP. Differences in the level of this signal molecule in the studied biological fluids, which are obtained from people of middle and elderly age, are not enough expressed. Significant differences ($P < 0.05$) are determined only in case of CAP for blood serum and oral fluid and in case of CAP + CHB for gingival fluid.

It can be assumed that the revealed regularity is associated with insignificant changes in the system of IL-1β expression in the transition of the body from middle to elder age.

Concentration of IL-6 in blood serum, oral fluid, and gingival fluid

Were liably established that the level of IL-6 in the oraland gingival fluids is indicative of the characteristics of the inflammatory immune response in patients with CAP. With the isolated course

of CAP, there was no significant increase in the content of this signal molecule in the blood serum of middle-aged patients. In the elderly patients, on the contrary, there was a significant increase in the content of this signal molecule in the blood serum. A further increase in polymorbidity led to a significant ($P < 0.05$) increase in the degree of inter leukinemia interms of IL-6.

The IL-6 content in the oral fluid is characterized by significantly higher absolute indices compared to the blood serum IL-6 content. With isolated flow of CAP, a significant increase is observed in the content of this signal molecule in the oral fluid in patients and middle-aged and elderly. A further increase in polymorbidity led to a significant ($P < 0.05$) increase in the degree of IL-6 interleukinemia.

In healthy middle-aged people, the concentration of IL-6 in the gingival fluid was significantly increased in the isolated course of CAP in patient soft the middle and elderly age. A further increase in polymorbidity led to a significant ($P < 0.05$) increase in the degree of IL-6 interleukinemia.

Data performed are shown in Table 4.

By its nature, IL-6 can act as a pro- and anti-inflammatory cytokine. It is synthesized by activated macrophages and T-cells and stimulates the immune response. IL-6 is one of the most important mediators of the acute phase of inflammation. As shown in Figure 3, the level of IL-6 in the oral and gingival fluids is the most indicative for characterizing the inflammatory immune response in case of CAP.

Cytokine levels in the same biological fluids reflect the influence of the increase of polymorbidity on the immune response of the body. It is typical that significant differences

Table 3: IL-1β content in blood serum, oral cavity, and gingival fluid, pg/ml

Studied indicator	Age	Signal molecule level			
		Healthy	CAP	CAP+CHF	CAP+CHF+type 2 diabetes
IL-1β in blood serum	Middle	191.1±22.4	195.5±23.7	269.8±29.8*,#	340.7±32.9*,#
	Elderly	193.2±20.2	255.0±21.0	315.4±29.1*,#	384.2±33.5*,#
IL-1β in oral cavity	Middle	170.1±21.4	174.2±22.0	245.1±27.4*,#	319.5±30.2*,#
	Elderly	171.4±21.0	230.0±21.2	293.8±28.1*,#	362.5±31.6*,#
IL-1β in gingival fluid	Middle	26.2±2.9	54.4±4.0	82.4±5.6*,#	115.6±7.3*,#
	Elderly	28.5±3.0	56.0±4.1	96.9±5.4*,#,○	129.0±7.7*,#

*$P<0.05$ compared to healthy people, #$P<0.05$ compared to patients with CAP, ○$P<0.05$ compared to middle-aged patients. CAP: Chronic apical periodontitis, IL: Interleukins

Table 4: IL-6 content in blood serum, oral cavity, and gingival fluid, pg/ml

Studied indicator	Age	Signal molecules level			
		Healthy	CAP	CAP+CHF	CAP+CHF+type 2 diabetes
IL-6 in blood serum	Middle	6.8±1.2	7.2±1.3	12.4±1.8*,#	17.9±2.0*,#
	Elderly	6.9±1.3	9.9±1.4	17.4±2.1*,#	23.2±2.3*,#
IL-6 in oral cavity	Middle	54.5±4.0	150.1±11.1	184.8±13.2*,#	216.8±15.6*,#
	Elderly	56.2±4.2	168.0±13.1	204.4±14.2*,#	261.6±19.8*,#
IL-6 in gingival fluid	Middle	5.4±1.0	21.6±2.1	36.4±3.6*,#	51.8±5.5*,#
	Elderly	5.6±1.1	24.0±2.3	39.8±3.9*,#	65.4±5.7*,#,○

*$P<0.05$ compared to healthy people, #$P<0.05$ compared to patients with CAP, ○$P<0.05$ compared to middle-aged patients. CAP: Chronic apical periodontitis, IL: Interleukins

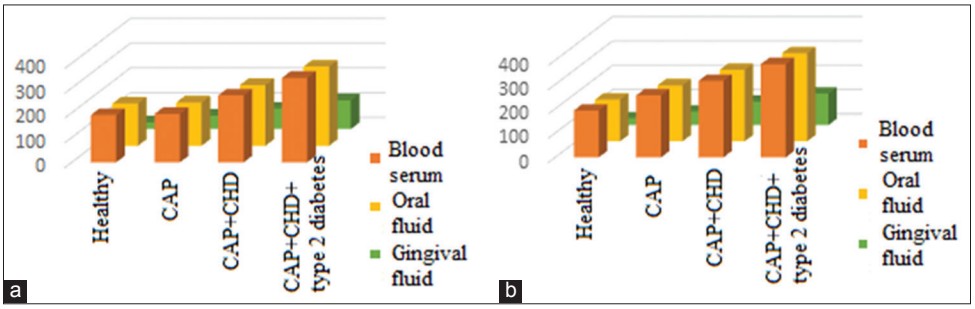

Figure 2: Concentration of interleukins-1β in various biological samples in middle-aged (a) and elderly, (b) patients with different degrees of polymorbidity (pg/ml)

in the level of IL-6 occur only in combination with CAP + CHD + type 2 diabetes or additionally with CAP + CHD in case of blood serum ($P < 0.05$). This fact directly indicates the relationship between age (middle or elderly) and the nature of polymorbidity effect on the level of the cytokine.

Concentration of IL-8 in blood serum, oral fluid, and gingival fluid

During the study of the concentration of IL-8, it was established that the magnitude of the proinflammatory reaction is age dependent with a tendency of a significant increase in the transition from the middle to the elderly age. On the level of the whole body, the pro-inflammatory system is moderately active and the degree of its activity correlates with the degree of polymorbidity. At the same time, on local level with CAP, pro-inflammatory system shows a very high level of activity in comparison to healthy people, which contributes to the progression of the pathological process.

IL-8 content in blood serum in elderly people is significantly ($P < 0.05$) higher than in middle-aged people. The increase in polymorphism leads to a significant ($P < 0.05$) increase in the degree of interleukinemia in terms of IL-8. It is important to note that a significantly higher level ($P < 0.05$) of serum IL-8 in elderly people compared with middle-aged people was observed in all cases studied.

The content of IL-8 in the oral fluid in patients with CAP significantly ($P < 0.05$) increased in people of both middle and elderly ages. Further increase in polymorbdity leads to a significant increase in the degree of interleukinemia in terms of IL-8 [Table 5].

The content of IL-8 in the gingival fluid in patients with CAP was significantly increased in people, both of middle and elderly ages. A further increase in polymorbidity leads to a significant increase in the degree of IL-8 interleukinemia.

It is important that a significantly higher level ($P < 0.05$) of IL-8 in the gingival fluid in elderly people compared with middle-aged people was observed in all studied cases of polymorbidity, as in the case of monopathology of CAP.

Data performed are shown in Table 5.

The obtained experimental data on the concentration of IL-8 in blood serum indicate that, in elderly patients, compared to the middle age, the activity of the pro-inflammatory system of the body increases significantly ($P < 0.05$). The increase in polymorbidity leads to an increase in this indicator both in the elderly and middle age. The concentration of IL-8 in the oral fluid indicates that, in the elderly, significantly ($P < 0.05$), the activity of the pro-inflammatory system in the local inflammatory focus in patients with CAP increases significantly

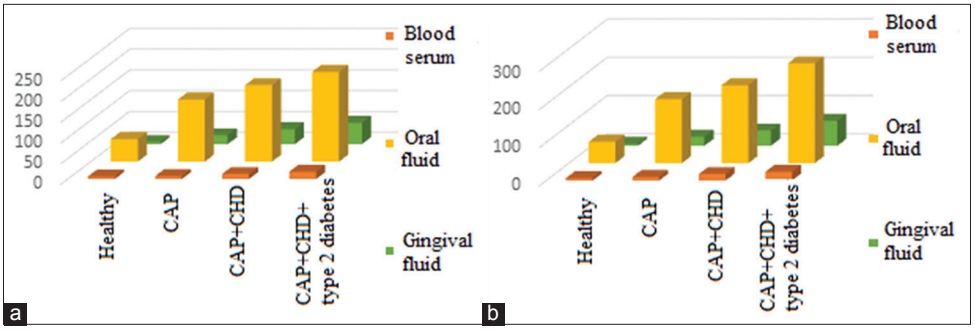

Figure 3: Concentration of interleukins-6 in different biological samples in people of middle (a) and elderly, (b) age with different degree of polymorbidity (pg/ml)

Table 5: IL-8 contentinbloodserum, oral cavity, and gingival fluid, pg/ml

Studied indicator	Age	Signal molecules level			
		Healthy	CAP	CAP+CHD	CAP+CHD+type 2 diabetes
IL-8 in blood serum	Middle	3.5±0.5	6.0±1.0	10.4±1.4*,#	16.6±2.0*,#
	Elderly	5.2±0.7	9.7±1.3	16.3±1.6*,#,○	20.4±1.7*,#,○
IL-8 in oral cavity	Middle	20.0±1.9	121.2±10.2	145.5±11.9*,#	179.9±13.0*,#
	Elderly	25.3±2.1	152.0±12.1	177.8±12.9*,#,○	215.0±14.1*,#,○
IL-8 in gingival fluid	Middle	15.0±1.4	90.1±8.1	112.6±9.8*,#	137.1±11.3*,#
	Elderly	18.4±1.5	110.3±9.7	134.0±10.5*,#,○	163.8±11.8*,#,○

*P<0.05 compared to healthy people, #P<0.05 compared to patients with CAP, ○P<0.05 compared to middle-aged patients. CAP: Chronic apical periodontitis, IL; Interleukins, CHD: Coronary heart disease

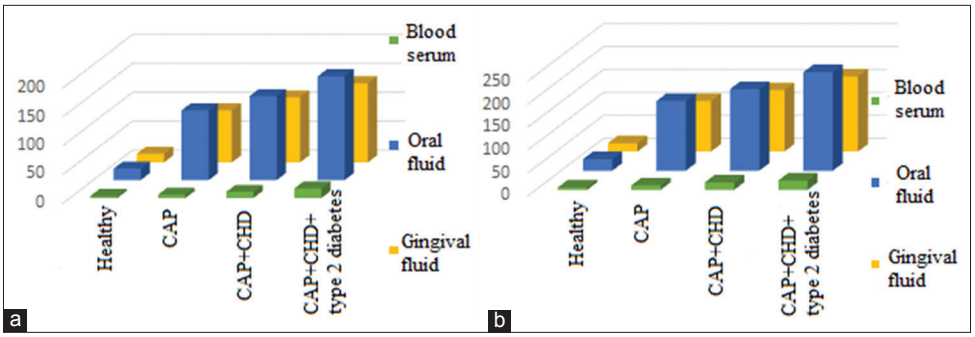

Figure 4: Concentration of interleukins-8 in different biological samples in people of middle (a) and elderly, (b) age with different degree of polymorbidity (pg/ml)

compared to the middle age. The increase in polymorbidity leads to a significant change of this indicator both in the elderly and middle ages. Consequently, the level of local pro-inflammatory response in CAP is largely determined not only by local factors but also by systemic ones.

The obtained experimental data on the level of IL-8 in the gingival fluid indicate that cells expressing this cytokine are located directly in the tissues (or next to them) that produce gingival fluid. Therefore, determining the level of pro-inflammatory response by the concentration of IL-8 in the gingival fluid can be informative.

In general, the severity of the pro-inflammatory reaction (judging by the concentration of IL-8) is age dependent with a tendency of a significant increase in the transition from middle to elderly age [Figure 4].

Thus, at the level of the whole body, the proinflammatory system is moderately active and the degree of its activity correlates with the degree of polymorbidity. At the same time, at the local level with CAP, pro-inflammatory system shows a very high level of activity (judging by the concentration of IL-8) compared with healthy people, which contributes to the progression of the pathological process.

CONCLUSION

- Concentration of TNF-α in blood serum with CAP can serve as an integral indicator of immune inflammation, while the local level of this cytokine in the oral and gingival fluid is less informative and is mediated by a fragmentary index of the general status of the neuroimmune system of the body.
- The level of IL-1β in blood serum, oral fluid, and gingival fluids can be considered as an additional factor characterizing the pathological process in polymorbid pathology, including CAP: CAP + CHD and CAP + CHD + type 2 diabetes.
- The level of IL-6 in the oral and gingival fluids is indicative of the characteristics of inflammatory immune response in patients with CAP.
- The severity of the pro-inflammatory reaction (judging by the concentration of IL-8) is age dependent with a tendency of a significant increase in the transition from middle to old elderly. At the level of the whole body, the pro-inflammatory system is moderately active and the degree of its activity correlates with the degree of polymorbidity. At the same time, at the local level with CAP, pro-inflammatory system shows a very high level of activity (judging by the concentration of IL-8) compared with healthy people, which contributes to the progression of the pathological process.

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