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The Role of Mineral Elements in The Pathogenesis of Lichen Planus of The Oral Mucosa.

Sergey Vasilevich Chuykin*, Gyuzel Maratovna Akmalova, Oleg Sergeyevich Chuykin, Natalia Vyacheslavovna Makusheva, and Galina Grigoryevna Akatyeva.

Bashkir state medical University, Russia, 450074, Ufa, Lenin st.,3

ABSTRACT

The content of trace elements in internal organs and environments reflect the homeostatic status of the body. They are very accurate and sensitive criteria that may signal the onset of its pathological changes. To study the role of some trace elements in the pathogenesis of lichen planus of the oral mucosa was performed to determine the contents of zinc, copper, iron and magnesium in blood serum and saliva in patients with lichen planus of the oral mucosa. In patients with lichen planus of the oral mucosa it was established the imbalance of the contents of some trace elements in blood serum and in oral fluid with pathological or adaptive in nature, which is of some importance in the pathogenesis of the disease. There is an interrelation of the level of microelements in blood serum and in oral fluid with the clinical form and severity of the disease. With increasing severity of the clinical course is observed a significant decrease in the level of zinc, copper, iron, and a statistically significant increase in magnesium content, mainly in the oral fluid, which in turn can aggravate the severity of lichen planus of the oral mucosa. The obtained data determine the pathogenic significance of the detected changes and allow raising the question of a possible correction of the mineral content, resulting in a deficit, by assigning the relevant mineral supplements.

Keywords: lichen planus, oral mucosa, microelements, zinc, copper, iron, magnesium, pathogenesis.

Corresponding author

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INTRODUCTION

Lichen planus of the oral mucosa (OLP) is characterized by predominantly relapsing, severe inflammatory reaction of tissues and a resistance to various therapeutic interventions. This is due to polyetiological and specific pathogenetic mechanisms of the development of this disease. Despite the variety of studies conducted by researchers, the etiology and pathogenesis of the disease remain the subject of much debate [1].

In the pathogenesis of inflammatory diseases one of the most important elements are the changes of the blood - tissue relationships aimed at restoring the disturbed homeostasis. There have been many hypotheses about regulatory mechanisms of homeostasis by influencing the transport of substances through biological barriers. Under the action of different environmental factors faced by people in contemporary socio-ecological conditions, most of the functional changes in the oral fluid are highly adaptive-compensatory in nature. Scientifical works have shown that determining the concentration of trace elements has a significant diagnostic value for the detection of systemic disease, even in preclinical stages [2]. The levels of macroelements and microelements in the internal organs and environments reflect the homeostatic status of the body, and are very accurate and sensitive criteria that may signal the onset of its pathological changes [3]. To study the role of some trace elements in the pathogenesis of LPOM was performed a determination of the content of zinc, copper, iron and magnesium in serum and in oral fluid of patients with OLP. This allows us to trace the flow of these chemical elements from the gastrointestinal tract into the blood and from the blood through the membranes of the salivary glands in the saliva and then in the oral fluid.

METHODS

In the conducted study were involved 191 persons with various forms of OLP (with a typical form - 43 patients, exudative – hyperemic form - 43, erosive-ulcer form - 47 patients, hyperkeratotic form - 24, atypical form - 28 patients, bullous form - 6 patients, 30 patients without OLP were included in the control group). The elemental composition of blood serum and oral fluid was determined by atomic absorption spectrophotometry in a flame of acetylene-air mixture.

Statistical processing of data was performed using the methods of medical biological statistics. To study the influence of several factor variables on the quantitative dependent characteristic, we used parametric analysis of variance.

The power of a factor`s influence, denoted by η2, indicates the proportion (in %) of the variability of the effective feature, which can be explained by one factor or a combination of several factors. To assess the significance of influence of factors on a productive indicator was used the Fisher test.

THE DISCUSSION AND RESULTS.

It is known that zinc is one of the most important trace elements which is involved in the growth and development of the epithelium. Even a slight deficiency of this element leads, in particular, to reduce the secretion of thymulin and interleukin-2 (IL-2). The change of zinc content in different biological fluids was demonstrated in patients with lichen planus [4]. However, the content of trace elements in a particular environment does not allow judging the state of element homeostasis in general.

Our research has shown that the zinc content in blood serum depended on the factor of a "group identity" of patients, – η^2=92%, F=423, p<<0.0001. So strong influence of this factor reflects the presence of sharp differences in the average level of this parameter between the control group and the groups of patients with OLP, as well as between all forms of OLP. The obtained data indicate (Table1) that the average level of zinc in the blood serum of the control group (16.2 ± 0.7 μg/DL) is about half or even two times higher than in all groups of patients with OLP. In addition, comparable with it in magnitude and statistically significant differences (p<0.05 or less) are occurred between all forms of OLP.

A similar situation occurred concerning of a zinc content in the oral fluid, which is also dependent on the "group membership"– η^2=71%, F=89, p<<0.0001. As in serum, in oral fluid among individuals of the control

group a zinc content was significantly higher (10.3 ± 1.1 µg/DL) than in groups of patients with OLP, and were also observed obvious differences between groups of patients with different forms of OLP.

The development of endogenous zinc deficiency leads to a violation of the processes of repopulation of cells and excessive apoptosis induction. As a result of this tissue metabolism is changing and a vascular wall is rebuilding. This further increases the needs in the costs of zinc and worsens its deficit.

Is forming a kind of vicious circle: lack of zinc in serum and in oral fluids causes damage of cells and intracellular structures in the oral cavity and maintains membrane inflammatory changes in the mucous. Clinically it is manifested by erosions and ulcers that do not heal for a long time, with a constant recurrence, with transition from one clinical form of lichen planus to another.

Another equally important trace element that is involved in many biochemical reactions, is copper. A determination of the copper content in the blood serum (η^2=66%., F=133, p<<0.001) showed that the level of copper depends on a group membership and there are significant differences between the control group and groups with different forms of lichen planus. In the control group the average level of copper in serum (118.2 ± 8.4 µg/DL) was higher than in any form of lichen planus.

The determination of the amount of copper in oral fluids revealed changes similar to the serum – η^2=58%, F=93, p<<0.0001. In another words, the average copper levels in oral fluid with all forms of lichen planus was significantly lower than in the control group (10.8 ± 1.5 µg/DL).

Table 1 - Contents of microelements in blood serum and oral fluid of patients with OLP

Elements		1group (n=43)	2 group (n=43)	3 group (n=47)	4 group (n=24)	5 group (n=28)	6 group (n=6)	Control (n=30)
Zn,	serum	12,3±0,6*	9,1±0,6*	8,1±0,7*	11,8±0,9*	9,9±1,2*	7,5±0,6*	16,2±0,7
µg/DL	oral liquid	7,7±1,8*	4,9±1,7*	3,9±1,3*	7,1±0,6*	5,5±1,2*	3,8±0,5*	10,3±1,1
Cu,	serum	105,3±11,3*	91,1±6,1*	75,0±14,5*	104,4±2,2*	98,4±3,8*	73,6±1,9*	118,2±8,4
µg/DL	oral liquid	9,2±1,8*	7,5±1,0*	5,4±1,1*	9,3±0,7*	8,4±0,7*	5,2±0,4*	10,8±1,5
Fe	serum	1018,0 ± 25,2*	1019,7±37,1*	1059,5±69,4*	1017,1 ± 15*	1021,6±23,1*	981,0±33,5*	1108,9±35,1
µg/l	oral liquid	331,6 ± 17,1*	251,8 ± 17,9*	188,1 ± 11,0*	314,0 ± 13,3*	321,7 ± 31,0*	190,2 ±22,3*	416,4 ± 11,0
Mg,	serum	23,9±5,1*	23,5±5,3*	23,5±6,1*	23,9±1,6*	23,1±1,2*	22,6±1,1*	21,5±3,2
µg/l	oral liquid	51,5±7,6*	45,5±9,96*	42,9±9,6*	50,8±4,85*	44,6±1,4*	44,4±1,8*	23,3±3,6

* - the accuracy in comparison with the control group

For the iron content in the serum a dependence from the factor of a "group identity" turned out to be quite significant – η^2=40%, F=23, p<<0.0001). There was a significant difference between iron content in the blood serum in the control group and in groups with different forms of lichen planus. The average levels for "typical", "exudative - hyperemic", "hyperkeratotic" and "atypical" forms were almost identical (1018 ± 25.2 µg/l, 1019.7 ± 37.1 µg/l, 1017.1 ± 15.1 µg/l, 1021.6 ± 23.2 µg/l, respectively) and, accordingly were not significantly different (p>0.72). In "erosive-ulcerative" and "bullous" forms of OLP the iron content in the serum was significantly higher and, respectively, lower than in other forms (1059.5 ± 69.4 mg/l, 981.0 ± 33.5 µg/l). Iron content in the oral fluid varied absolutely different. The dependence of this parameter from the factor of a "group membership" was very strong (η^2=94%, F=637, p<<0.0001). This dependency is generated by the sharp difference between the control group (416.4 ± 11.0 µg/l) and all groups with different forms of OLP, as well as by equally sharp differences between some of these groups (Table1).

Some scientific publications indicate that the lichen planus is often accompanied by a deficiency of vitamin B12, folic acid, iron, vitamins B1 and B6 [5], and also shows the relationship between iron deficiency in the blood and the severity of the lichen planus [6]. The results of this study are largely consistent with these

data. An important feature of the detected changes, in our opinion, is a marked reduction of iron concentration in oral fluid at an almost normal level in the blood serum. It is not excluded that low iron levels in the oral fluids affects the course of the inflammatory process, contributing to the transition of OLP in more severe forms. This assumption is confirmed by the relationship between the severity of clinical course of the disease and iron levels in oral fluid.

Completely different values occurred for the content of magnesium in the blood serum. The dependence of this parameter from the factor of a "group identity" was not statistically significant ($F=1.02$, $p>0.41$). This is due to the lack of significant differences in the average levels of magnesium among all groups. A significant difference ($p<0.03$) was determined between the control group (21.5 ± 3.2 μg/l) and the group with "hyperkeratotic" form of lichen planus (23.9 ± 1.6 μg/l). In oral fluids a content of magnesium was also dependent on the factor of a "group identity". It was strong enough – $\eta^2=58\%$, $F=50$, $p<<0.0001$. This is primarily due to the strong difference between the average level of this parameter in the control group (22.3 ± 3.6 μg/l) and in overall of almost two-fold higher values in all forms of lichen planus.

Trace elements, directly or indirectly, play an important role in various metabolic processes of the human body. More than 25% of the enzymes contain metal ions in their active center, allowing them to carry out metabolic functions [7]. For example, copper and zinc are involved in redox processes, in the maintenance of the proton potential in the cell. The copper is presented in the active center of many enzymes that are involved in the oxidative processes, such as ceruloplasmin, aminooxidase, cytochrome oxidase. Zinc is a part of the active center of carbonic anhydrase and proteolytic enzymes (carboxypeptidases, lacinaminopeptidases, metalloproteinases) [8].

Diseases of the oral mucosa are a reflection of systemic diseases of the body and are detected in almost all segments of the human population in the world. Most diseases of the oral mucosa are treatable, but some of them disrupt the function of organs and tissues of the mouth, which undoubtedly leads to the deterioration of the quality of life of patients. Zinc is one of the most important minerals of the human body, has many functions in the life of cells, such as growth and division, is involved in collagen synthesis and wound healing [9,10]. Zinc deficiency is accompanied by numerous physiological abnormalities. They affect the condition of the mucous membrane of the oral cavity. Literature data regarding the level of zinc in serum and oral fluid of patients with diseases of the oral mucosa are few and controversial [11,12,13].

It is shown that a decrease in level of zinc ions in saliva is associated with the operation suppression of the oxidant - antioxidant system [14,15]. Zinc also participates in regulation of cell cycle and cell division, as it is a part of the active site of DNA polymerase. Zinc ions regulate signals of transduction, gene expression and apoptosis of cells [16]. In the blood plasma zinc is bound to albumin and then it is transported to its destination. Excess of iron suppresses the ion concentration of zinc and copper through the blockade of iron – dependent transport systems. The level of zinc ions in plasma is constant and does not depend on the intake of the zinc with food. Cells of the salivary glands, prostate, immune system and intestine use zinc as signaling molecules in intercellular interactions [17].

Zinc is a cofactor in about 3000 different proteins, including regulatory, therefore in humans zinc deficiency may be accompanied by the development of various pathological states [9,18,19]. It is shown that zinc deficiency has a positive correlation with diseases of the oral mucosa. Inflammation of the tongue, which is associated with food deficiency, iron deficiency, vitamin B12 and hemoglobin, is characterized by low content of zinc in the blood of patients in 25% of cases [5,6]. The high prevalence of zinc deficiency in the blood was detected in patients with lichen planus [4], glossitis [20] and xerostomia [21]. While in women the levels of zinc were lower [22,23]. Clinicians suggest that the appointment of zinc supplementation for these patients may be successful in the treatment of diseases of the oral mucosa. They do not take into account the risk of side effects because of the high levels of zinc in the body [24]. So, D. A. Wray et al [25] is not recommended to use zinc-therapy in patients with precancer of the oral cavity. Other studies have shown that additional supplementation of zinc, on the contrary, reduced the development of glossitis.

Copper plays an important role in tumor angiogenesis, especially in the early stages of its development. Copper is required for activation and increase of endothelial cells. Copper ions activate some angiogenic factors (growth factor of a vascular endothelium, tumor necrosis factor-alpha, interleukin – 1, fibroblast growth factor-beta) that are associated with transition of endothelial cells from the G0 to the G1

phase and cause cell proliferation [26]. Copper is involved in fibrillogenesis via copper dependent enzyme lysyloxidase, which is involved in the linking of collagen and elastin. Various studies have revealed a dysregulation of the enzyme activity of lysyloxidase, which leads to the formation of excessive cross-linking in the collagen molecule, which is not hydrolyzed by collagenase [27].

Copper and iron are involved in the regulation of the reduction of oxygen supply by an indirect effect on the aerobic respiration enzyme - cytochrome C oxidase.

Iron in the body is involved in many reactions of biological oxidation and executes transport functions. The reduction of the level of iron ions is apparently associated with its active role in the reaction of hydroxylation of Proline on the stage of posttranslational modifications of collagen synthesis. Iron deficiency in the organism is accompanied by the formation of a thin layer of epithelium, which is susceptible to environmental factors. Iron ions are also actively involved in the formation of the vascular bed, and its deficiency leads to the increased vascular permeability and reduced vascularization of tissues. Consequently, the inflammatory response of the affected tissue dies, and fibrous bands are formed [28].

In the saliva the copper ions are increased in the case of hyperkeratosis. The highest levels of copper ions in the saliva were recorded in individual forms of lichen planus – bullous, erosive and hyperplastic. In the case of cancer and precancer the number of copper ions in the saliva is reduced [29]. And in the case of leukoplakia of the oral cavity the indicators of zinc ions and copper ions did not differ from control values. In another study in saliva of patients with submucous fibrosis, leukoplakia, lichen planus was showed a significant increase in the levels of zinc and copper [30].

Magnesium is necessary for the body trace element. It plays a role in stabilizing cell membranes and nerve conduction. Magnesium is essential for the functioning of all energy-dependent transport systems, glycolysis and oxidative phosphorylation, it affects the platelet aggregation and electrolyte balance, has a relaxing effect on the smooth muscle wall of the vessels. Magnesium deficiency induces a chronic impairment of a redox status that is associated with inflammation. This may contribute to the increase of free radical oxidation of lipids and proteins. Lack of magnesium inhibits the growth and migration of the endothelium, stimulates the synthesis of nitric oxide and several proinflammatory cytokines in vivo, thus directly affecting the microvasculature [31]. Magnesium is a mandatory and full participant in the inflammatory response, and a deficiency of this element is able to trigger and maintain the inflammatory response, to create the conditions for the activation of autoimmune processes and free radical oxidation.

Magnesium preparations have found wide application in a complex therapy of inflammatory diseases, including lichen planus. It is possible that the increase in magnesium content in serum and oral fluid of patients, and the decrease ratio in comparison with the control values are a reflection of a nonspecific compensatory response aimed at implementation of the inflammatory response as a result of a treatment that is aimed at reducing the inflammatory response, the content of magnesium in the blood serum and oral fluid, as well as the value of the ratio of the magnesium were closer to normal. We should pay attention to the fact that, in our study, despite of significant changes in the levels of the studied elements in blood, in almost all examined groups of patients with OLP they did not go beyond the boundaries of generally accepted reference values. Keeping in mind this fact, the detected changes can be interpreted as pathological or adaptive imbalance of trace elements when in the presence of an active inflammatory process is formed their relative scarcity both in the blood, and especially in the oral fluid.

CONCLUSION

Based on identified changes of microelement status of the following it can be stated:

- In patients with OLP is found the imbalance of the content (pathological or adaptive in nature) of some trace elements in blood serum and in oral fluids, which is of some importance in the pathogenesis of the disease.
- There is an interrelation of the level of microelements in blood serum and in oral fluids with the clinical form and severity of the disease. With the increasing of a severity of the clinical course is observed a significant decrease in the level of zinc, copper, iron, and statistically significant increase in magnesium content, mainly in the oral fluid, which in turn can aggravate the severity of OLP.

The obtained data determine the pathogenic significance of the detected changes and allow us to raise the question of a possible correction of the mineral content, resulting in a deficit, by assigning the relevant mineral supplements.

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