The Concept of Blood-Tissue Barriers in Dentistry

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Abstract

Between the blood and the organs, between the blood and tissues there are special barriers (blood-tissue barriers), which represent the multilevel security system of the organism, aimed at providing general and local homeostasis. The protective function of organs and tissues that are protected by blood-tissue barriers is realized by the changes of the permeability barrier for certain substances and is quantitatively estimated by the permeability coefficient (PC). In-depth studies of the functioning of blood-tissue barriers in lichen planus of the oral mucosa (LP OM) are relevant today. But they have not been conducted yet. In patients with LP OM was found a violation of a permeability condition of the blood-tissue barriers for some mineral elements (zinc, copper, iron, magnesium), which is of importance in the pathogenesis of the disease. This manifests itself in multidirectional changes in mineral composition of blood serum and oral fluid, which correlate to the severity of the clinical course of the disease. Thus, the definition of pathogenetic importance of the detected changes will allow solving the issue of a possible correction of the mineral content, resulting in a deficit, by assigning mineral supplements. The expected effects can be a relief of the clinical course of the process, a more rapid healing of erosions and ulcers in the mouth, improvement of the general condition of patients and improving their quality of life.

Key words: lichen planus, oral mucosa, zinc, copper, iron, magnesium, pathogenesis, blood-tissue barriers, and permeability.

INTRODUCTION

The idea of the internal (tissue) barriers is a consistent development of ideas about the constancy of the internal environment of the body. A total internal medium (liquid base of the body according to Cannon) for all organs and tissues is blood. But the cells of organs do not contact with blood. Each organ has its own microenvironment – the tissue (interstitial) or the extracellular fluid, which is the nutritional environment of organs and tissues [1].

L. S. Schtern for the first time suggested that between the blood and the organs, between the tissues there are the special barriers (blood-tissue barriers), which represent the multilevel security system of the organism, aimed at providing general and local homeostasis. They regulate the transition from the blood into the interstitial fluid of the substances required for respiration, nutrition, growth and change of cells, at the same time contribute to the removal from the microenvironment of the intermediate products of metabolism [1].

Given the location of the barriers they are divided into blood-brain (between blood and brain), blood-ophthalmic (between blood and eye tissue), placental (between mother`s organism and fetus), blood-salivary (between the blood and the internal environment of the salivary glands), etc [1].They are all differing from each other in their physiological properties and structure.

A morphological substrate of the blood-tissue barriers in the oral mucosa are the endothelial cells of blood vessels, secretory cells of the salivary glands, the cells of the excretory ducts of the salivary glands, accompanying their myoepithelial cells, and also the extracellular matrix lamina propria of the mucous membrane consisted of collagen and elastic fibers, the space between which is filled with a gel-like substance, and is largely determining the transport processes in the interstitial space [2].

Myoepithelial cells with their processes are covering outside the secretory cells and intercalated ducts, and their contraction promotes the excretion of saliva. The excretory ducts in the norm are surrounded by a quaggy fibrous connective tissue, which is also contributing to transport processes.

The permeability of blood-tissue barriers is selective. They pass into the interstitial fluid of the body only certain substances - this defies explanation by the laws of physics or chemistry, only the physiological significance for the organism of these substances is taken into the consideration [1].

The activity of any organ is largely determined by the state of the barrier, and the accurate and smooth operation of the entire barrier system contributes to maintaining of homeostasis in general. But the barriers do not only protect the organs and tissues from harmful substances. They also regulate the flow to the organs of blood components (proteins, fats, carbohydrates, salts, minerals) which are necessary for their nutrition and metabolism. They are active and plastic, their permeability can vary depending on the requirements of the cells.

The protective function of organs and tissues which are protected by blood-tissue barriers is realized by changes of the permeability barrier for certain substances and is quantitatively estimated by the permeability coefficient (PC) [1].

Permeability – is one of the properties of the barrier, it is an indisputable mechanism of its functioning, and is regulated by morphological, physical, chemical, and physiological factors.

The permeability of the blood-tissue barriers is the result of the activity of its anatomic elements, it explains the particular selectivity, which does not completely disappear, but it only changes in some pathological

conditions: the permeability may increase for some substances and may decrease or simply do not change for the others [1,3].

The in-depth studies of the functioning of blood-tissue barriers in lichen planus of the oral mucosa (LP OM) were not conducted, and that is relevant today. This is due to the increase in the incidence of LP OM among the population, to the increasing phenomenon of the manifestation at a young age, to increase in the rate of severe and treatment-resistant clinical forms [4]. Often the disease is recurrent, continuous with short periods of remission. To date, the pathogenetic mechanisms of occurrence of lichen planus of the oral mucosa (LP OM) remain unclear and are the subject of wide discussion by dentists and dermatologists [4,5,6,7,8,9].

METHODS.

To study the functioning of blood-brain barriers in the LP OM in our study were involved 191 persons with various forms of the disease (with typical - 43 patients, exudative - hyperemic - 43, erosive - 47 patients, hypertrophic - 24, atypical form - 28 patients, bullous - 6 patients), 30 people without the LP OM were included in the control group. The elemental composition of blood serum and oral fluid (zinc, copper, iron, magnesium) was determined by atomic absorption spectrophotometry in the flame of acetylene-air. Then, in order to determine the directional transport of these mineral elements, that are reflecting the functioning of the blood brain barriers, was calculated the ratio of serum / oral fluid.

Statistical processing of data was performed using the methods of biomedical statistics. To study the influence of several factor variables on the quantitative dependent characteristic, we used parametric analysis of variance. The power of influence factor, denoted by η^2, indicates the proportion (%) 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 RESULTS AND DISCUSSION.

The ratio serum / oral fluid (η^2=10%, F=4, p<0.001) was depended on the factor of "group identity". In particular, the average levels of PC in the control group, in the "typical" and in "hyperkeratotic" groups were quite close (1.58 ± 0.18, 1.67 ± 0.39 and 1.68 ± 0.17, respectively) and were not significantly different (p>0.7). However, is noticeable an upward trend in the ratio during the transition from "typical" forms to the "exudative-hyperemic" and then to the "erosive-ulcerative" (1.67 ± 0.39, 2.20 ± 1.11 and 2.64 ± 2.27, respectively), as well as from "hyperkeratotic" to "atypical" and "bullous" (1.68 ± 0.17, 1.86 ± 0.28 and 2.02 ± 0.28, respectively). In the first group of patients with the typical form of LP OM a gradual increase in the ratio was statistically significant, however the differences in the ratio of patients with "exudative-hyperemic" and "erosive-ulcerative" form turned out to be unreliable (p>0.08) (figure 1).
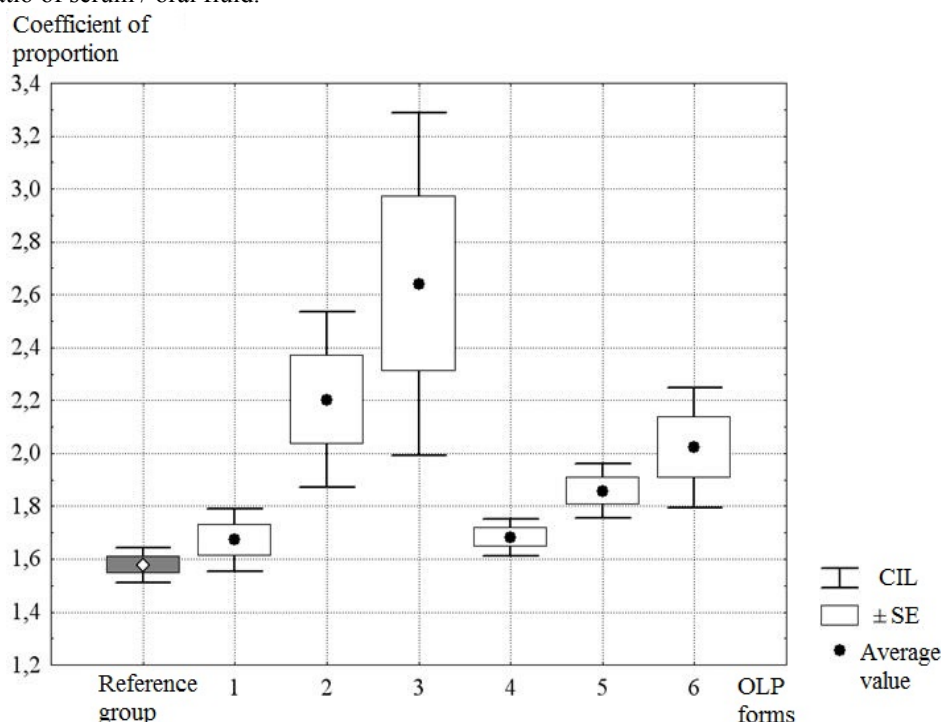

Figure 1 - Odds ratios (coefficient of proportion) serum / oral fluid for zinc in groups of patients with different forms of LP OM before the treatment.

Y-axis - values of the ratio. The abscissa shows control group (reference group), forms of LP OM (OLP forms): 1 – a typical form, 2 - exudative-hyperemic, 3 - erosive-ulcerative, 4 - hyperkeratotic, 5 - atypical, 6 - bullous form. CIL – confidence limits for the average values (CIL - confidence interval limit), SE - standard error of the mean (SE - standard error of average value).

It should be noted that the feature of these two forms of LP OM is a sharp (fold) increase of intra-group variability. Therefore, the reliability of differences was evaluated using the nonparametric criterion of Mann-Whitney. The test showed that the observed apparently quite marked differences in levels of PC between these forms of LP OM were not statistically significant (p>0.06). The difference of PC levels "atypical" and "bullous" forms was insignificant according to U-criterion (p>0.51). However, the buildup of the ratio at these forms of LP OM relative to the control group and the group with "hyperkeratotic" form was significant for all criteria.

The analysis of the value of PC has allowed establishing significant changes of functional activity of blood-tissue barriers. A significant increase of its functional activity with reduced permeability to zinc was determined in patients with severe clinical course of LP OM.

Copper is equally important trace element involved in many biochemical reactions.

The dependence of the ratio of serum / oral fluid for copper upon the factor of "group identity" was weaker (figure 2), although it was significant (η^2=13%, F=9.9. p<<0.0001).

The average values of PC were significantly increased from "typical" forms to the "exudative-hyperemic" and then to the "erosive-ulcerative" (11.2 ± 2.3, 12.0 ± 1.5 and 13.0 ± 3.2, respectively), as well as from "hyperkeratotic" to "atypical" and "bullous" (11.0 ± 0.7, 11.5 ± 0.8 and 13.6 ± 1.8, respectively). The average ratio for copper was close or almost coincide in pairs "typical" – "hyperkeratotic", "exudative-hyperemic" – "atypical" and "erosive-ulcerative" – "bullous". Differences in mean levels in these pairs were statistically insignificant – p>0.68, p>0.06 and p>0.93, respectively. For the last pair the difference was also insignificant for the Mann-Whitney test (p>0.39).

The ratio of serum/oral fluid reflects transport function of blood-tissue barriers for the trace element - copper.

Patients with LP OM with a severe clinical course had a higher value of the ratio for copper, indicating a reduction in the permeability of the blood-tissue barriers for copper and a violation of its targeted transport into the oral fluid.
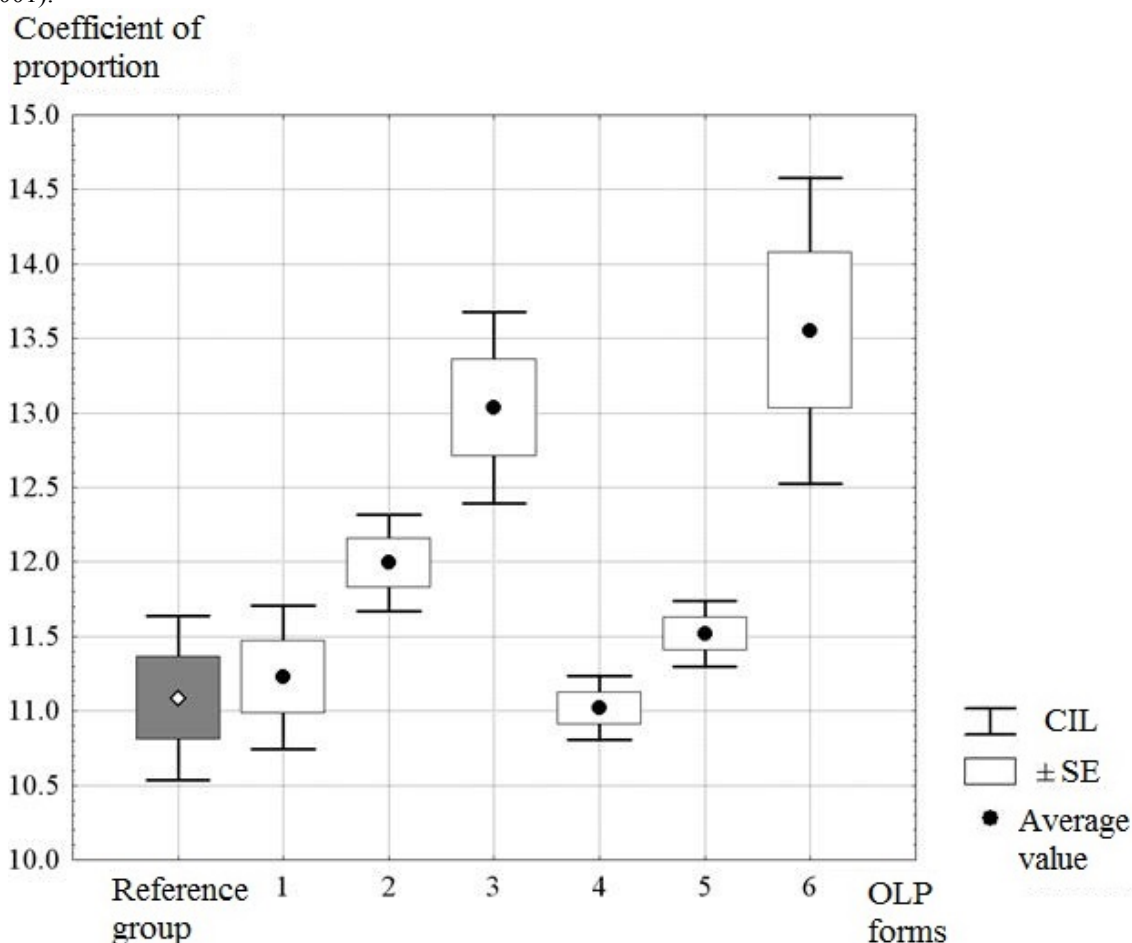

Figure 2 - Coefficients of correlation of serum / oral fluid for copper in groups of patients with different forms of LP OM before the treatment.

Y-axis - values of the ratio. The abscissa shows control group (reference group), forms of LP OM (OLP forms): 1 – a typical form, 2 - exudative-hyperemic, 3 - erosive-ulcerative, 4 - hyperkeratotic, 5 - atypical, 6 - bullous form. CIL – confidence limits for the average values (CIL - confidence interval limit), SE - standard error of the mean (SE - standard error of average value).

On the value of the ratio for zinc and copper, the clinical manifestations of LP OM in patients with severe disease (erosive-ulcerative, bullous, exudative-hyperemic forms) differed from the clinical manifestations in patients with a mild form of LP OM (typical form).

In relation to the ratio of serum/oral fluid for iron is observed a pattern (η^2=86%, F=629, p<<0.0001) (figure 3). The level of the ratio for all forms of LP OM is higher than in the control group (2.66 ± 0.11). The ratio for iron is increasing substantially and significantly from "typical" forms of LP OM to the "exudative-hyperemic" and then to "erosive-ulcerative" (3.08 ± 0.17, 4.06 ± 0.26 and 5.64 ± 0.36, respectively). In "bullous" form the value of the ratio (5.21 ± 0.50) is very close to the ratio in the "erosive-ulcerative" form, although is significantly below it. The difference of the levels of the ratio in these cases was confirmed by the Mann-Whitney test (p<0.03).

In "hyperkeratotic" and "atypical" forms the values of PC are close (3.24 ± 0.12 and 3.20 ± 0.29, respectively) and do not differ significantly (p>0.56).

According to the ratio of serum/oral fluid was evaluated the functioning of the blood-tissue barriers for iron.

Patients with LP OM with a severe clinical course had a higher value of the ratio for the iron, similarly as for zinc and copper, which showed a decrease in the permeability of the blood-tissue barriers for the iron and the violation of their targeted transport into the oral fluid. This allows assuming that the main contribution to the differences in the ratio is due to a difference in the amount of trace element in the oral fluid.

In scientific publications it was shown that the LP is often accompanied by a deficiency of vitamin B12, folic acid, iron, vitamins B1 and B6 [10], and also shows the relationship between iron deficiency in the blood and severity of LP [11]. 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 possible to conclude about the permeability of the blood-tissue barriers in the ratio of iron: the ratio of iron in all the surveyed groups of patients was significantly higher than the control values, indicating that the decrease in the rate of transport of iron to the saliva. It is not excluded that the low iron levels in the oral fluids affects the course of the inflammatory process, contributing to the transition of LP OM 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.
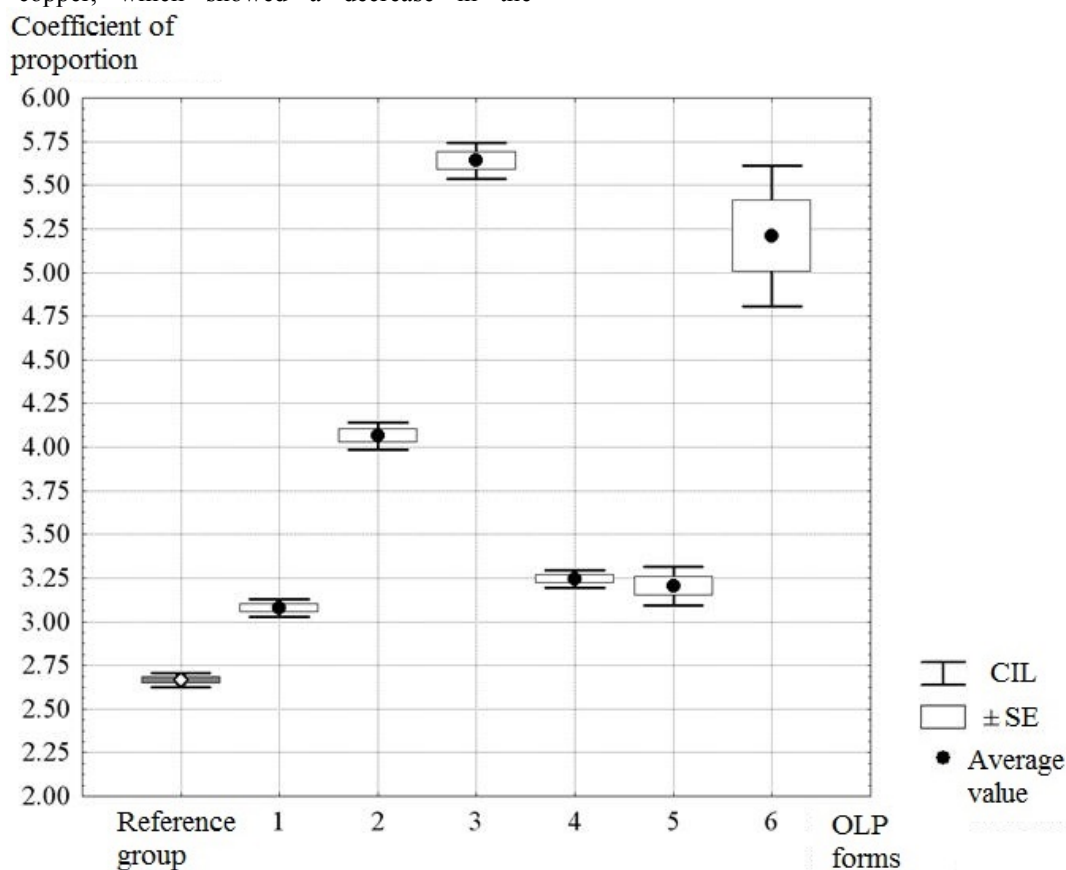

Figure 3 - Coefficients of correlation of serum / oral fluid for iron in groups of patients with different forms of LP OM before the treatment.
Y-axis - values of the ratio. The abscissa shows control group (reference group), forms of LP OM (OLP forms): 1 – a typical form, 2 - exudative-hyperemic, 3 - erosive-ulcerative, 4 - hyperkeratotic, 5 - atypical, 6 - bullous form. CIL – confidence limits for the average values (CIL - confidence interval limit), SE - standard error of the mean (SE - standard error of average value).

The dependence of the value of the ratio of serum/oral fluid for magnesium upon the factor "group identity" $\eta^2=62\%$, F=59, p<<0.0001 (figure 4): the maximum average value of PC (0.94 ± 0.16) was detected in the control group. The value is almost twice that for all forms of LP OM. And also is well marked the statistically significant tendency to the increase in the average level of the ratio from "typical" forms of LP OM to the "exudative-hyperemic" and then to "erosive-ulcerative" form (0.47 ±0.08, 0.52 ± 0.14 and 0.56 ± 0.14, respectively). The average ratio for "atypical" and "bullous" forms were almost identical and were not significantly different (0.52 ± 0.03 and 0.51 ± 0.02, p>0.85). The ratio for "typical" and "hyperkeratotic" forms of LP OM (0.47 ± 0.08 and 0.48 ± 0.06, p>0.81) was almost identical. Thus, although in the form of a mirror the picture of group distributions of values of the ratio resembles the distribution of magnesium content in the oral fluid. It also allows us to believe that for the value of the ratio, like iron and magnesium, to the greatest extent influences the content of this trace element in the oral fluid.
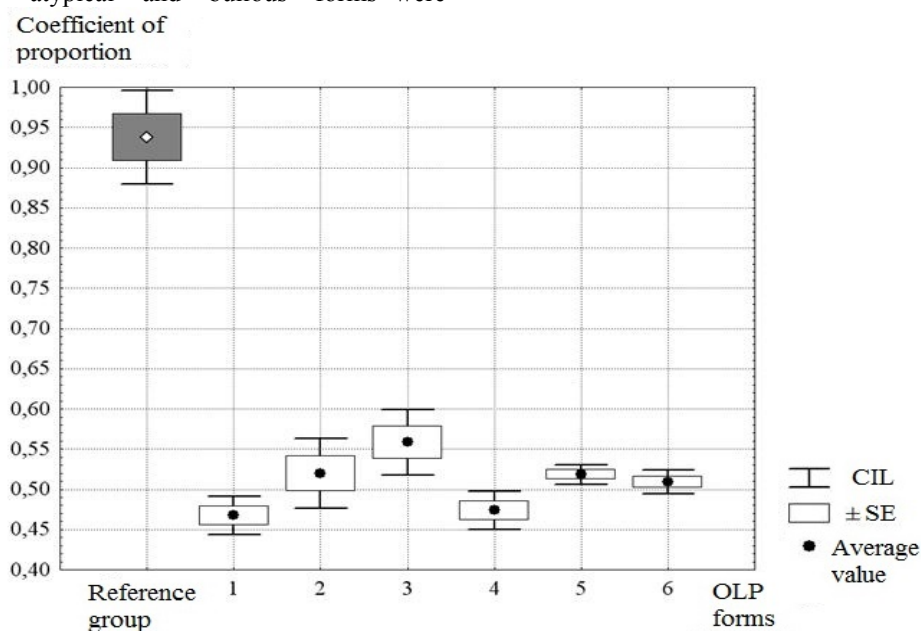

Figure 4 - Coefficients of correlation of serum / oral fluid for magnesium in groups of patients with different forms of LP OM before the treatment.

Y-axis - values of the ratio. The abscissa shows control group (reference group), forms of LP OM (OLP forms): 1 – a typical form, 2 - exudative-hyperemic, 3 - erosive-ulcerative, 4 - hyperkeratotic, 5 - atypical, 6 - bullous form. CIL – confidence limits for the average values (CIL - confidence interval limit), SE - standard error of the mean (SE - standard error of average value).

CONCLUSION.

In patients with LP OM was found a violation in condition of permeability of the blood-tissue barriers for some mineral elements (zinc, copper, iron, magnesium), which is of importance in the pathogenesis of the disease. This manifests itself in multidirectional changes in mineral composition of blood serum and oral fluid, which correlate to the severity of the clinical course of the disease.

Thus, the definition of pathogenetic importance of the detected changes will allow solving the issue of a possible correction of the mineral content, resulting in a deficit, by assigning mineral supplements. And the expected effect can be a relief of the clinical course of the process, the more rapid healing of erosions and ulcers in the mouth, the improvement of the general condition and the quality of life of patients.

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