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Structural-functional determinants of vitamin D status and hematological indicators in patients with chronic recurrent aphthous stomatitis

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Chronic recurrent aphthous stomatitis (CRAS) is one of the most common diseases of the oral mucosa. Although its etiology is not fully established, it is known that vitamin and mineral deficiency can be a trigger. Since vitamin imbalance and vitamin deficiency are also important in the genesis of CRAS, epithelial insufficiency was studied depending on the level of vitamin D in CRAS patients living in the northwestern region of Ukraine. Since the level of vitamin D, which is produced almost exclusively under the influence of ultraviolet radiation, affects the processes of hematopoiesis, erythropoiesis, the number of erythrocytes in peripheral blood and the erythrocyte intoxication index were determined. Erythrocytes were studied in relapse of CRAS using scanning electron microscopy and morphometry. Based on the statistical analysis of erythrocyte diameters, it was established that wave fluctuations of erythrocytes are excited in relapse of CRAS. The amplitude and frequency of these fluctuations in advanced CRAS were higher due to an increase in the number of echinocytes, in which lipid melting, membrane fluidity and surface tension are enhanced. Some changes in the geometric parameters of erythrocytes were observed, in particular, elongation and narrowing of discs, deepening of central pits, and reduction of membrane roughness. Porous structures were also subject to transformation: there was an increase in the diameter of the pores, depth and volume, smoothing of the membrane relief, a decrease in the surface of the ultra thickness of the channels, an increase in the number of cone-shaped pores. The quantitative indicators of macroelements of erythrocytes (sodium, calcium, magnesium and chlorine) were increased, and the potassium content was reduced. As a result of the multidirectional action of deforming forces, the membranes of erythrocytes were unevenly smoothed, forming centers of seals with a hydrophobic surface and depressions with hydrophilic boundaries, which increases the heterogeneity of the structure and speed of hydrodynamic flows. In expanded pores with smooth walls, the flows become limited and accelerated, in depressions - they slow down and become turbulent. As a result, the pressure on the bottom and walls increases in the depressions, and their boundaries dissolve, sticky particles of detritus accumulate. This effect is called "creeping" erosion and the associated risks of aggregation determine the harmful effect of shock waves during the period of recurrence of CRAS. These changes lead to the formation of microthrombi, respectively, a certain area of tissue is excluded from the blood circulation, which, against the background of a decrease in the level of immunity, leads to increased erosion of the oral mucosa and causes the development of local manifestations of CRAS.

Keywords: oral diseases; chronic recurrent aphthous stomatitis; Vitamin D deficiency; vitamin D insufficiency; erythrocytes; erythrocyte membranes; scanning electron microscopy.

Introduction

One of the most common diseases of the oral mucosa is chronic recurrent aphthous stomatitis (CRAS) (Natah et al., 2004; McCullough et al., 2007; Wang et al., 2018), which, unlike dental caries and periodontal diseases, is currently not preventable (Rivera, 2019). In the general population, CRAS occurs in 5–25% of the population of different age groups, with a tendency to increase its frequency (Field & Allan, 2003; Scully & Porter, 2008; Oluwadaisi et al., 2023). CRAS is a chronic inflammatory disease of the oral mucosa, manifested by the periodic appearance of single or multiple painful ulcers. The disease occurs with periodic remissions and frequent exacerbations, accompanied by periodic fever or chronic subfebrility, which negatively affect the quality of life of a person. The etiology of CRAS remains unknown (Belenguer-Guallar et al., 2014), so the relevance of research does not lose its sharpness. The etiology and pathogenesis of CRAS are considered as a multifactorial process caused by various provoking factors and immunological disorders. Possible triggers include mucosal injury, food allergy, genetic predisposition, stress, as well as hematite deficiency and vitamin deficiency (Brustad et al., 2007; Tugrul et al., 2016). It is believed that diseases of the oral mucosa can occur when patients are deficient in vitamin D, an important steroid hormone with immunomodulatory, membrane-stabilizing, epithelializing, anti-inflammatory and antibacterial effects (Siregar et al., 2023). Vitamin D is produced almost exclusively under the influence of ultraviolet (UV) radiation, which has the greatest impact on health. The wavelength range responsible for vitamin D photosynthesis, i.e. the *in vivo* action spectrum and the absorption spectrum of 7-dehydrocholesterol (the precursor of vitamin D), is known with considerable certainty. The action spectrum of vitamin D generation is important for the immunological effects of solar radiation, due to which interaction with the immune system occurs (Moan et al., 2009).

Vitamin D status, as noted by a number of researchers (Goldstein et al., 1970; Zakharov & Tyrnov 2001; Rosen et al., 2012), is determined by variations in solar ultraviolet radiation depending on the season of the year and the geographical latitude of the territory, which cause the morbidity of various organs and systems. Evidence is presented that geographical latitude is an additional stress for the immune system, which is involved in almost all human diseases (Davis & Lowell, 2006). Solar energy is a powerful biological factor, fluctuations in the amount of which cause changes in organic properties, important physiological phenomena, in particular in the rate of chemical and physiological reactions, increasing the total number of pathological processes (Juzeniene & Moan, 2012).

Although to date there is not sufficient understanding of the basic interaction of the effects of solar insolation and the subsequent photobiology and photochemistry of vitamin D synthesis in humans, it has been established that low levels of vitamin D (25(OH)D) in the blood serum are associated with the development of a wide range of diseases (Kimlin, 2008; Bogomaz & Shatylo, 2023; Chen et al., 2024). The determinant of a decrease in vitamin D status is lower exposure to solar insolation. The greater the change in solar insolation during the year (the smaller the ratio between the minimum and maximum monthly values), the greater the probability of the first episode of numerous disorders (Bauer et al., 2022). In addition to seasonal fluctuations, a decrease in the efficiency of endogenous photosynthesis of vitamin D through the epidermis of human skin occurs with age and also depends on the diet (consumption of fish products with vitamin D), which is important for the prognosis of the onset and course of pathological processes (Moan et al., 2009).

The status of vitamin D in the body is assessed by the optimal marker by determining 25(OH)D in blood serum. Today, there are approaches to determining vitamin D deficiency and insufficiency, formed on the basis of clinical practice recommendations of the Endocrine Society (Holick et al., 2024) and on the basis of recommendations for the prevention and treatment of vitamin D deficiency (Płudowski et al., 2023). The Endocrine Society has proposed the following ranges for vitamin D status: vitamin D deficiency (serum 25(OH)D $\leq$ 20 ng/mL or $\leq$ 50 nmol/L), vitamin D insufficiency (21–29 ng/mL or > 50 and < 75 nmol/L), and normal vitamin D level ($\geq$ 30 ng/mL or $\geq$ 75 nmol/L) (Holick et al., 2024).

Serum 25(OH)D levels as a reflection of vitamin D status (deficiency or insufficiency) remain common in many countries around the world (Dabek-Szreniawska, 1970; Edvardsen et al., 2007; Lips et al., 2021). Thus, a number of studies have shown that the average rate of vitamin D deficiency in the world is about 37%, with the highest rates in European countries (40%), especially in Western Europe (30–60%), and Africa (34%), and the lowest rates in the United States (18%) (Crowe et al., 2019; Bouillon, 2020). Based on the results of multinational studies conducted in countries located at different latitudes, vitamin D insufficiency has been found in Germany (Hintzpeter et al., 2008), Italy (Adami et al., 2009), France (Castetbon et al., 2009), Slovakia (Vanuga et al., 2009), Canada (Schwalfenberg et al., 2010), Spain (Almirall et al., 2010), Great Britain (Adams & White, 2015), Poland (Płudowski et al., 2016), Belgium (Moyersoen et al., 2017), Ireland (Scully et al., 2023).

In Ukraine, epidemiological studies on vitamin D status were conducted in the period 2011–2019, which established a high level of its deficiency and insufficiency among the population of Ukraine, regardless of age, gender and region of residence (Povoroznyuk et al., 2011). Ukraine is the largest European territory, covering different climatic zones, and 37.3% of the population may have vitamin D deficiency (< 10 ng/mL), which is a very high proportion compared to other European countries (Povoroznyuk & Balatska, 2022). It was found that only 4.6% of Ukrainian residents have a level of 25(OH)D within the normal range, 13.6% have its insufficiency, and 81.8% have vitamin D deficiency (Shchubelka, 2020). At the same time, the average level of 25(OH) D in Ukraine was 13.87 ng/mL, and the lowest (12.61 ng/mL) in the western part of Ukraine, which geographically includes the Rivne region. Only 4% of residents of the western region of Ukraine have a sufficient level of vitamin D (Shchubelka, 2020).

It is known that iron plays an important role in the metabolism of vitamin D, which is involved in many enzymatic systems in the body. It is worth noting that UV deficiency leads to a deterioration in the use of copper and iron by the body, a decrease in their level in hematopoietic and other organs, and a deterioration in hematopoiesis, which under appropriate climatic conditions must be taken into account in the daily diet (Gabovich et al., 1975; Kimlin et al., 2007). A number of experimental studies demonstrate the effect of ultraviolet rays on intestinal iron absorption, erythropoiesis, erythrocyte number and lifespan, and submicroscopic structure of erythrocytes (Kabat et al., 1971; Dańieyko-Osman, 1975; Mietkiewski et al., 1983). The effect of ultraviolet radiation on human erythrocytes, which was evaluated *in vitro* at different intensities, demonstrated a dose-dependent effect of UV radiation, which can be used to assess its biological effects (Misra et al., 2005). Monitoring the intensity of solar UV-B and artificial UV-B on human erythrocytes showed a difference in their phototoxicity and dose dependence, with artificial UV radiation causing hemolysis of erythrocytes significantly more often than solar UV (Klinke, 1973; Kumar et al., 2009). However, it has been reported that hemoglobin released as a result of chronic hemolysis in patients with sickle cell anemia alters the absorption of vitamin D carrier, impairs the absorption and metabolism of the vitamin, contributing to its deficiency (Gliozzi et al., 2019). A number of studies have suggested that a lack of sunlight exposure may be more dangerous to human health, as vitamin D deficiency is associated not only with rickets and osteomalacia, but also with an increased risk of cardiovascular disease, rheumatoid arthritis, type 1 diabetes, Crohn's disease, multiple sclerosis, tuberculosis, influenza, and many types of cancer (Juzeniene et al., 2011; Hewison, 2012).

So far as it is known, vitamin D, in addition to regulating calcium and phosphate metabolism, also performs other physiological functions, including immunological ones (Chennamashetti & Muley, 2020). Regarding the relationship between vitamin D and the immune system, it is now clear that immune cells contain all the mechanisms necessary to convert 25-hydroxyvitamin D into active 1,25-dihydroxyvitamin D. These mechanisms contribute to the antimicrobial response to pathogens in macrophages and to the regulation of hematopoietic cell maturation (Charoenngam & Holick, 2020). Vitamin D, entering the bloodstream, is converted by the kidneys into the active form, which, by binding to the vitamin D receptor (VDR) in the nucleus, performs its physiological functions in the target tissue. There are reports that the use of vitamin D together with physical exercise significantly reduced hyperglycemia in experimental animals caused by diabetes mellitus, contributed to a significant increase in the number of erythrocytes, hematocrit, hemoglobin, erythropoietin and a decrease in the number of leukocytes (Abdulrahim et al., 2024).

Vitamin D intake is positively correlated with increased blood hemoglobin levels (Chennamashetti & Muley, 2020). In addition, vitamin D has been found to directly increase erythropoietin sensitivity in people with impaired renal function, and vitamin D deficiency is associated with hyperparathyroidism, which leads to reduced endogenous erythropoietin production (Osunkwo et al., 2011). A significant positive correlation of vitamin D_3 with serum hemoglobin in patients with sickle cell anemia has been established (Chennamashetti & Muley, 2020). A positive correlation between serum 25-hydroxyvitamin D levels and biomarkers of hemolysis (hemoglobin/hematocrit) has also been demonstrated (Adegoke et al., 2018). Although iron and vitamin D deficiencies are among the most common health problems in the world, current knowledge about their deficiencies is limited to the study of bone metabolism and remodeling at osteoporosis (Al-Daghri et al., 2022).

Recent studies have shown that iron metabolism in the body is closely related to the metabolism of certain trace elements and vitamins in patients with CRAS (Piskin et al., 2002; Lopez-Jornet et al., 2014). The clinical and morphological criteria of iron and B vitamin deficiency-induced oral mucosa are well-studied. There are reports of a predisposition to recurrent CRAS episodes associated with vitamin B_1, B_2, B_6, B_{12} and iron deficiency (Queiroz et al., 2018; Robier et al., 2018), as well as with an abnormal decrease in the number of circulating erythrocytes (Daley & Armstrong, 2007). There is no data in the available scientific literature on changes in peripheral blood erythrocytes (PBE) at CRAS, although they, along with leukocytes, occupy a significant place in the etiopathogenesis of inflammatory-necrotic lesions of various tissues, including oral mucosa.

The study of iron and vitamin D status in patients with CRAS is of great interest, since the relationship between the level of 25(OH)D and iron deficiency in the genesis of CRAS is still unknown. Therefore, the purpose of our study was to evaluate the relationship between the level of vitamin D, iron deficiency anemia, morphometric indicators of peripheral blood erythrocytes and their influence on the formation of epithelial insufficiency in patients with chronic recurrent aphthous stomatitis living in the northwestern region of Ukraine.

Materials and methods

During the study, the bioethical norms of the World Medical Association Declaration of Helsinki "Ethical Principles of Medical Research Involving Human Subjects" (adopted by the 59th General Assembly, revised in October 2008), the Declaration of Ethical Principles of the Ukrainian Helsinki Union for Human Rights (2016), the International Code of Medical Ethics and the Laws of Ukraine (decision of the Bioethics Commission of the I. Horbachevsky Ternopil National Medical University (protocol No 75 dated November 1, 2023)). The study was conducted on the basis of the municipal non-profit enterprise "City Dental Polyclinic" of the Rivne City Council. The purpose of the study was explained to patients with CRAS who were included in the study, after which they signed an informed consent form. 83 patients aged 20–45 years participated in the study. The main group consisted of 61 people with clinical history of recurrent aphthous ulcers; control group – 22 healthy individuals. According to the clinical picture of CRAS, small, large and herpetiform ulcers were classified. Dental examination of patients was performed using general clinical methods. Given the importance of regional climate features of the region, from the life history of the subjects we found that all patients with CRAS permanently lived in the Rivne region – the northwestern region of Ukraine.

Considering the influence of solar ultraviolet rays on the efficiency of endogenous synthesis of vitamin D and its status as a key factor of numerous components of innate and adaptive immunity, we determined the level of 25-hydroxyvitamin D in the blood serum of patients with CRAS and control group individuals. The level of 25-hydroxyvitamin D (25(OH)D) in blood serum was measured by electrochemiluminescent immunoassay on an automatic analyzer Cobas e411 (Roche Diagnostics, Basel, Switzerland, 2019). The cut-off values for blood serum 25(OH)D levels were as follows: vitamin D deficiency, < 50 nmol/L; moderate deficiency, 25–50 nmol/L; severe deficiency, < 25 nmol/L; vitamin D insufficiency, 50–75 nmol/L; vitamin D sufficiency, 75–250 nmol/L; optimal concentration, 75–125 nmol/L; elevated level, 125–250 nmol/L; and toxicity, ≥ 250 nmol/L. Depending on the vitamin D deficiency level, the distribution of patients with different forms of CRAS changes. The conducted dental examination of patients showed that among patients with CRAS, 70.5% (n = 43) were diagnosed with small aphthous ulcers; 27.9% (n = 17) patients had large aphthous ulcers and 1.6% (n = 1) had herpetiform ulcers (Table 1).

Table 1
Distribution of patients by vitamin D level depending on the form of CRAS

Vitamin D level, nmol/L	Forms of CRAS		
	small aphthous ulcers (n = 43)	large aphthous ulcers (n = 17)	herpetiform ulcers (n = 1)
< 25	1	2	1
25–50	7	4	–
50–75	27	10	–
75–250	4	1	–
75–125	2	–	–
125–250	2	–	–

A blood laboratory test was performed to determine the content of erythrocytes and the level of hemoglobin on an automatic hematology analyzer BC-5150 (Mindray, Guangzhou, China, 2018) and we calculated the erythrocyte intoxication index (EII). Morphometric parameters of peripheral blood erythrocytes (PBE), their metric redistribution (ratio of different forms of erythrocytes in the blood – reversibly and irreversibly deformed cells) were studied using scanning electron microscopy. Peripheral blood cell preparations for scanning electron microscopy were prepared according to the generally accepted technique immediately after smear preparation. Different metric forms of erythrocytes were detected using a scanning electron microscope "JEOL-TA-25-220" (JEOL Ltd., Tokyo, Japan, 2006), their images were analyzed at different magnifications of the microscope in the UTHSCSA Image Tool® editor (Schindelin et al., 2012). The content of important chemical elements of peripheral blood erythrocytes was determined using X-ray microanalysis with an "EDAX" analyzer and an accelerating voltage of 10 kV, which the electron microscope was equipped with. Peripheral blood erythrocytes were pre-coated with a carbon layer up to 10 nm thick on a magnetron sputtering installation "VUP-6M" (VO Selmi, Sumy, Ukraine, 2000). The data presented in the tables as x ± SD (mean ± standard deviation). The difference between groups was considered statistically significant based on the results of the Mann-Whitney U test at $P < 0.05$.

Results

We found that the average value of the concentration of 25 (OH) D in the blood serum of healthy individuals was 51.53 ± 6.32 nmol/L, i.e. it was within the limit values of the levels – "vitamin D insufficiency". In patients with CRAS, the mean serum 25(OH)D concentration was 27.31 ± 4.12 nmol/L, which can be classified as "moderate deficiency". A statistically significant difference in vitamin D levels was found between the two groups. The distribution of vitamin D status in the examined CRAS patients was as follows: severe deficiency – 6.6% (n = 4), moderate deficiency – 18.0% (n = 11), vitamin D insufficiency – 60.7% (n = 37), vitamin D sufficiency – 8.2% (n = 5), optimal concentration – 3.3% (n = 2), elevated level – 3.3% (n = 2). Depending on the vitamin D deficiency level, the distribution of patients with different forms of CRAS changes (Table 1). We found that with increasing degree of vitamin D deficiency , there is an increase at the number of patients with severe forms of CRAS.

Since the level of vitamin D affects the processes of hematopoiesis, erythropoiesis, the number of erythrocytes and their lifespan, as well as the submicroscopic structure of erythrocytes, we conducted the following studies. Since deficiency of hematological indicators is among the possible triggers of the occurrence and recurrence of CRAS, we determined the most important indicator of the characteristic and the most numerous morphological elements of the blood – the number of erythrocytes. The amount of oxygen that is received by the tissues of the body to ensure the necessary biochemical processes in them depends on the number and function of erythrocytes and hemoglobin.

The analysis of the number of erythrocytes we conducted demonstrated a decrease in the indicator in patients with CRAS. Thus, the degree of erythrocytopenia according to clinical blood analysis of patients with CRAS ranged from (3.1–3.4) 10^{12}/L (with normative values of (4.0–5.1) 10^{12}/L in men and (3.7–4.7) 10^{12}/L in women). The decrease in the number of erythrocytes in patients with CRAS with vitamin D deficiency varied: it was slightly reduced (3.4 10^{12}/L) in 23 people (37.7%) and significantly reduced (3.1 10^{12}/L) in 35 people (57.4%). In 4.9% of cases (n = 3), the number of erythrocytes was within the normative values.

Since the lesion of epithelial cells of the esophageal mucosa is accompanied by an increase in the level of endogenous intoxication, we assessed the erythrocyte intoxication index. Thus, in the main group of examined patients, the EII was 55.16 ± 0.64, which is 2.24 times higher than the control group (24.68 ± 0.32). The obtained results of the study showed that aphthous stomatitis is accompanied by an increase in the endotoxicosis marker – the erythrocyte intoxication index during the period of manifestation of CRAS. At the same time, the toxic effect is diverse and manifests itself at the level of cells and tissues. Some components of this pool of substances inhibit gluconeogenesis and deoxyribonucleic acid (DNA) synthesis, inhibit erythropoiesis and suppress the production of blood hemoglobin. Thus, in the vast majority (95.1%) of the patients with CRAS examined by us, a decrease in the number of erythrocytes in the blood was confirmed as the main criterion for anemia.

Although the prevalence of anemia has often been used as a proxy indicator of iron deficiency anemia, an integrated, multifactorial approach is necessary in diseases of unknown etiology. The data from our electron microscopic study of peripheral blood cells will help to significantly expand the understanding of the morphological structure of peripheral blood erythrocytes in patients with CRAS.

Thus, we have established that the linear dimensions of peripheral blood erythrocytes of the most numerous (70.5%) group of CRAS patients with small aphthae are characterized by minor but systemic disturbances. In particular, the sizes of peripheral blood erythrocytes differ only in the tendency to decreased diameters, but more significant and statistically significant differences are observed along the short axes (Table 2). The central pits of the discs deepen, but at the same time the thickness of the discs decreases by 50–75 μm, which is due to a decrease in the thickness of the protein-globular layer of the peripheral blood erythrocytes' wall. The data of the table indicate minor deviations of each parameter (no more than 5–7%), but they accumulate and become systemic, which makes these changes functionally significant.

Table 2
Morphometric parameters of peripheral blood erythrocytes in patients of the control group and patients with small aphthous ulcers (x ± SE)

Parameters of erythrocytes	Groups of patients	
	control group (n = 22)	patients with small aphthous ulcers (n = 61)
Disk diameter, µm	6.50 ± 0.11	7.01 ± 0.32***
Disk height, µm	0.785 ± 0.048	0.339 ± 0.016**
Depth of central pits, µm	425.4 ± 15.2	311.8 ± 13.8***
Form factor – D_{max}/D_{min}, conditional units	1.01 ± 0.01	1.12 ± 0.08**
Pore diameter, µm	122.5 ± 9.9	163.9 ± 11.7***
Pore depth, µm	62.3 ± 5.3	79.7 ± 7.8***
Relative pore surface area, µm^2	82.4 ± 7.7	73.4 ± 6.7***

Note: two groups were compared using oneway ANOVA: * – P < 0.05; ** – P <0.01; *** – P <0.001 – relative to the control group.

The study of morphometric indicators of peripheral blood erythrocytes and their metric distribution in patients of the control group showed that the erythrogram of the distribution of peripheral blood erythrocytes by the average cell size has a unipolar appearance. In patients of this group, the distribution of erythrocytes by their diameters was as follows: 4 µm – 2.4%, 5 µm – 4.8%, 6 µm – 6.4%, 7 µm – 84.5% and 8 µm – 1.9%. Thus, the volume of size classes in the left small-sized wing (4–6 µm) is only 13.6%. The median of the sample – the average value of the diameter feature – was 7.09 ± 0.31 µm.

To better reflect the dispersion of indicators by erythrocyte diameters in the pathological process, we determined the interval every 0.5 µm. In persons with CRAS, it was found that the erythrogram of the distribution of PBEs by their diameter is asymmetric and multipolar due to an increase in the number of varying classes of the left wing, in which the volume of size classes is 70.2%. Thus, the distribution of erythrocytes by diameters looks as follows: 4.0–4.5 µm – 13.7%, 5.0–5.5 µm – 18.4%, 6.0–6.5 µm – 38.1%, 7.0–7.5 µm – 26.5%, 7.5–8.0 µm – 3.3%. At the same time, an increase in the number of PBEs of the left wing is accompanied by a decrease in the value (to 5.5 ± 0.3 µm) of the median of the sample. The specified features of the morphometric indicators of erythrocytes mean that in CRAS, PBEs of small sizes react first of all, which is characteristic of short-term reactions. These reactions develop rapidly and, apparently, occur as a result of the withdrawal of cells of the "first echelon of defense" from the reserve pool of the general bloodstream.

The distribution of PBEs in patients with CRAS demonstrates an increase in the number of intervals, the volumes of individual classes, which vary due to jumps. At the same time, the achievement of the values of the central parameters occurs in a wave-like manner, unlike the indicators of the control group, where the indicators of the central parameters follow a monotonically upward trend. The pathological form of the erythrogram, apparently, reflects the unstable-oscillating state of PBEs during the active phase of CRAS due to a large number of microorganisms and toxic products of their metabolism.

Under the influence of adverse factors, the system enters a deterministic state, in which the PBEs seem to "compress" and go to a monomorphic unimodal state. It can be assumed that the PBEs themselves undergo elastic deformation, and the oscillations, in amplitude and frequency, become higher than the initial ones. As a result of the increase in the frequency of oscillatory oscillations, the stable state of the cell membrane is unbalanced. PBEs begin to stretch, which corresponds to higher values of the form factor – generalized factors that affect the change in the conformation of PBEs from normal to reversibly or irreversibly changed forms.

Changes in the physical state of membrane lipids are accompanied by a decrease in the roughness and specific surface area of the membranes. This means that the surface tension in the PBE membranes increases and, accordingly, the surface energy decreases, which contributes to the formation of a large number of abnormally transformed erythrocytes.

The increase in surface tension is also facilitated by the compaction of the peripheral blood erythrocytes, which is observed with an increase in the weight indices of sodium, calcium, magnesium, and chlorine against the background of a decrease in the concentration of potassium, which tends to leave the cells under the action of mechanical forces (Table 3). Differences in the concentration of sodium and potassium on different sides of the erythrocyte membrane ensure the functioning of numerous intracellular enzymes. The release of K^+ through the Na^+/Cl^- cotransport system can contribute to pathological dehydration of erythrocytes. Violation of the balance between these elements can contribute to pathological dehydration of erythrocytes and lead to their pathological conformation.

Table 3
Biochemical indicators of peripheral blood erythrocytes according to energy-dispersive X-ray microanalysis in the control group and patients with CRAS (x ± SE)

Parameters	Groups of patients	
	control group (n = 22)	patients with small aphthous ulcers (n = 61)
Sodium/potassium	0.271 ± 0.007	0.410 ± 0.002*
Magnesium/potassium	0.0348 ± 0.0013	0.0525 ± 0.0029***
Chlorine/potassium	1.023 ± 0.004	1.284 ± 0.008**
Calcium/potassium	0.00519 ± 0.00236	0.00791 ± 0.00375***

Note: see Table 2.

As a result of the action of surface tension forces caused by the influence of the above-mentioned chemical elements, the membranes straighten, become stronger against rupture. At the same time, in the surface layers of the walls of the peripheral blood erythrocytes, foci of compaction appear, which morphologically have the appearance of degranulated areas protruding 50–80 nm above the surface. Although the mechanisms of formation of such areas are unknown, with relapse of CRAS the area of the foci of compaction increases almost twice compared to the norm of specific area. Against the background of increasing oscillatory deformations of the peripheral blood erythrocytes and surface tension forces, the processes of formation of capillary waves in the transmembrane fluid are certainly enhanced, the speed of their movement will increase as the surface tension increases, and the length will decrease due to the thinning of the discs. The described relationships create structural and physical-mechanical prerequisites for high-frequency shift of oscillating vibrations of intracellular fluid and membrane structures of the peripheral blood erythrocytes.

The intensity of transmembrane exchange, in particular, the speed of hydrodynamic flows, is largely determined by the structure and shape of the pores. At CRAS, the diameter of the entrance, depth and relative volume of the pores in the membranes of erythrocytes are significantly higher than the control values, i.e., the membranes become more porous, and, accordingly, more permeable (Fig. 1). This occurs in a jump-like manner not only due to expansion, but also through the formation of pores de novo. Expanded pores have raised edges formed by grains of different caliber with a subgranular organization. Most pores in patients with CRAS have a funnel-shaped shape, although normally, in the control group, funnel-shaped pores are less common, and their diameter does not exceed 150 nm. In the peripheral blood erythrocytes of patients with CRAS, the funnel-shaped pores are larger in diameter (up to 250 nm), their bottom is covered with a thin layer of sticky liquid and paved with orderly arranged granules, the space between which is expanded and forms a large-scale network of interconnected ultrathin channels. The mouths penetrate deeply into the multilayered walls of the peripheral blood erythrocytes.

As a result of the multidirectional action of deforming forces, the membranes are straightened unevenly – large (up to 300 µm in diameter), but shallow (15–25 µm) depressions appear. The raised edges of the depressions are characterized by significant height differences, pierced by twists (meanders) and slopes, the appearance of such structures indicates a slowdown in the flow of transmembrane fluid. Twists are loop-like bends of the bottom with a length of up to 50–100 µm, which dissect the walls of the depressions, the edges of which are slightly turned out and can rise up to 100 µm in height.

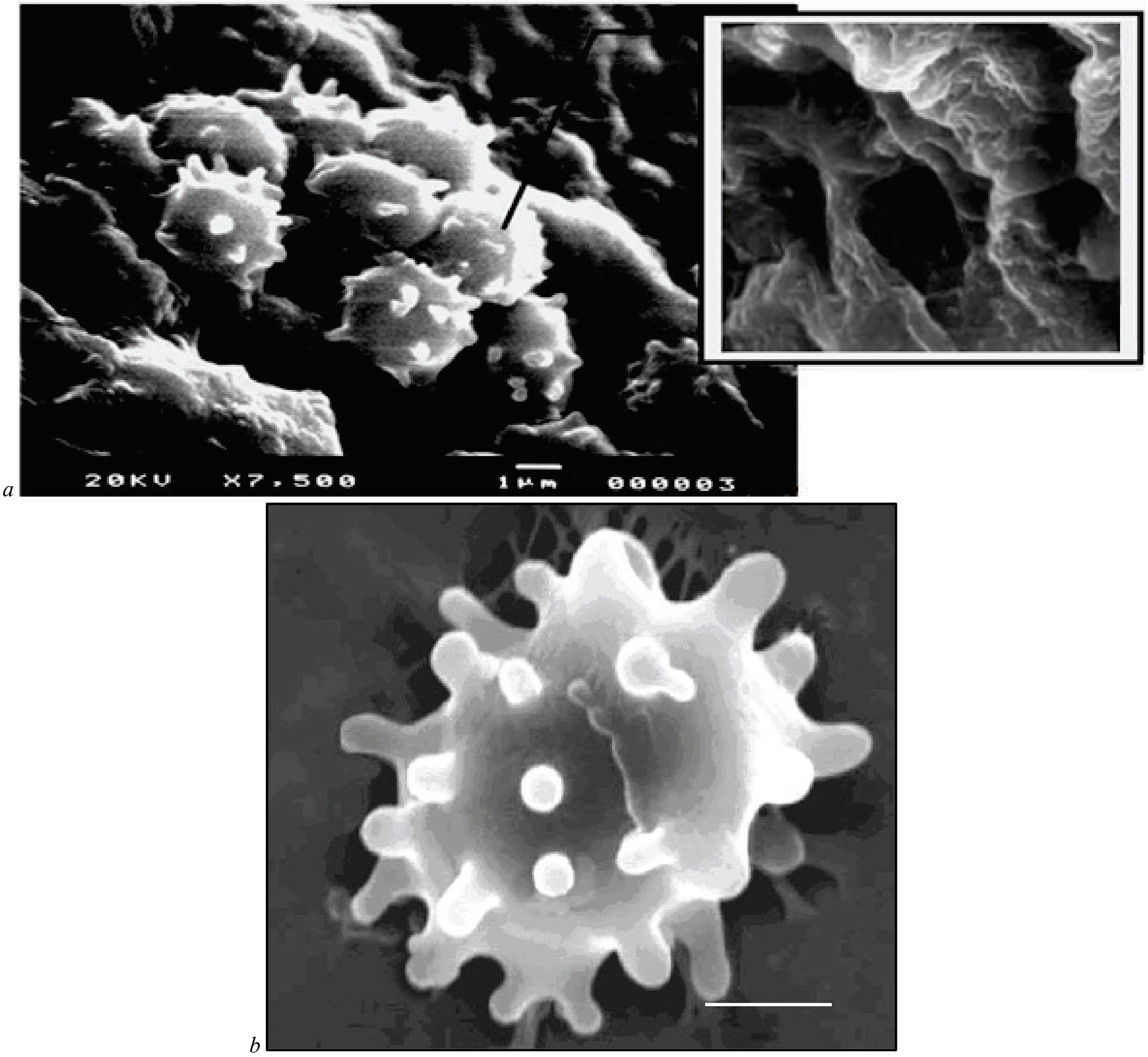

Fig. 1. General appearance of irreversible forms of peripheral blood erythrocytes (echinocytes) and pores in their membrane (footnote) in patients with CRAS: *a* – accelerating voltage 20 kV, scale bar = 1 µm; *b* – accelerating voltage 25 kV, scale bar =1 µm

The slopes are mainly convex, which complicate the microrelief with two-three-tiered formations, the steps of which expose the structure of the walls of the peripheral blood erythrocytes. SEM study of the bottom of the cavities in the absorbed electron mode allows us to see in fine detail the surface texture, to detect nanochannels that form a dense branched network, and detritus particles of varying degrees of dispersion in the form of polymorphic agglutinates. The surface of the cavities, especially in the area of the spongy bottom, is highly adhesive, which indicates the accumulation of viscous fluid in it. The described changes in functional terms mean the orientation of the peripheral blood erythrocytes to preferentially remove the substance. In the pathomorphological sense, such changes are regarded as preparation for pyroptosis – a type of apoptosis, during which cells throw out (splash out) cytoplasmic material.

The above morphological features complicate the texture of the surface of erythrocyte disks. This determines the heterogeneity of the speeds and structures of intra- and transmembrane hydrodynamic flows. When a liquid passes through expanded pores with a relatively smooth relief of the walls, the flow speed increases, unlike in small depressions with branched edges, where the speed of hydrodynamic flows slows down and the flow becomes turbulent. When the speed (kinetic energy) of hydrodynamic flows decreases, the pressure and, accordingly, the friction created on the walls and bottom of the depressions increase. The circulating transmembrane fluid begins to stagnate, "sludge", turning into a viscous fluid that dissolves the bottom and walls. As a result, the depressions turn into membrane defects that develop by the mechanism of "creeping" erosion.

Thus, at CRAS, there is a modification of the morphological characteristics of erythrocytes – a universal reaction of erythrocyte membranes to disruption of the mechanisms of regulation of metabolic processes, which is accompanied by a change in the morphofunctional characteristics of erythrocytes. Depending on the deformation resistance of erythrocytes, the nature of their shape changes (Fig. 2).

Normally, the peripheral erythron is represented exclusively by discoid erythrocytes, and the patient has a fully functional cluster. However, the reactive state of the erythron can change in pathological conditions as a result of the appearance of echinocytes in the peripheral blood. Their pathophysiology is determined by the fact that an environment enriched with Ca^{+2} ions is formed around echinocytes, which is a trigger factor for the aggregation of discocytes (normocytes) around them and the formation of fibrin threads. These changes lead to the formation of microthrombi, respectively, a certain area of tissue is excluded from the blood circulation, which in turn causes increased erosion of oral mucosa.

All morphological changes of peripheral blood erythrocytes of patients with CRAS determine the degree of contamination of oral mucosa with pathogenic microflora (Fig. 3). Thus, SEM examination of the oral mucosa surface in patients of the control group shows polygonal epithelial cells with clear boundaries and practically absent microflora. The presence of irregularly located microridges surrounding numerous pits is observed. In patients with CRAS, microorganisms similar to mycoplasma are found attached to the surface of the oral mucosa epithelial cells. Some microorganisms, apparently, penetrate through the cells, others accumulate in the intercellular spaces.

Our results show that low vitamin D levels and morphological changes in the peripheral blood erythrocytes may be associated with CRAS, as patients also have significantly higher mucosal colonization with coccal and fungal microflora (Fig. 4).

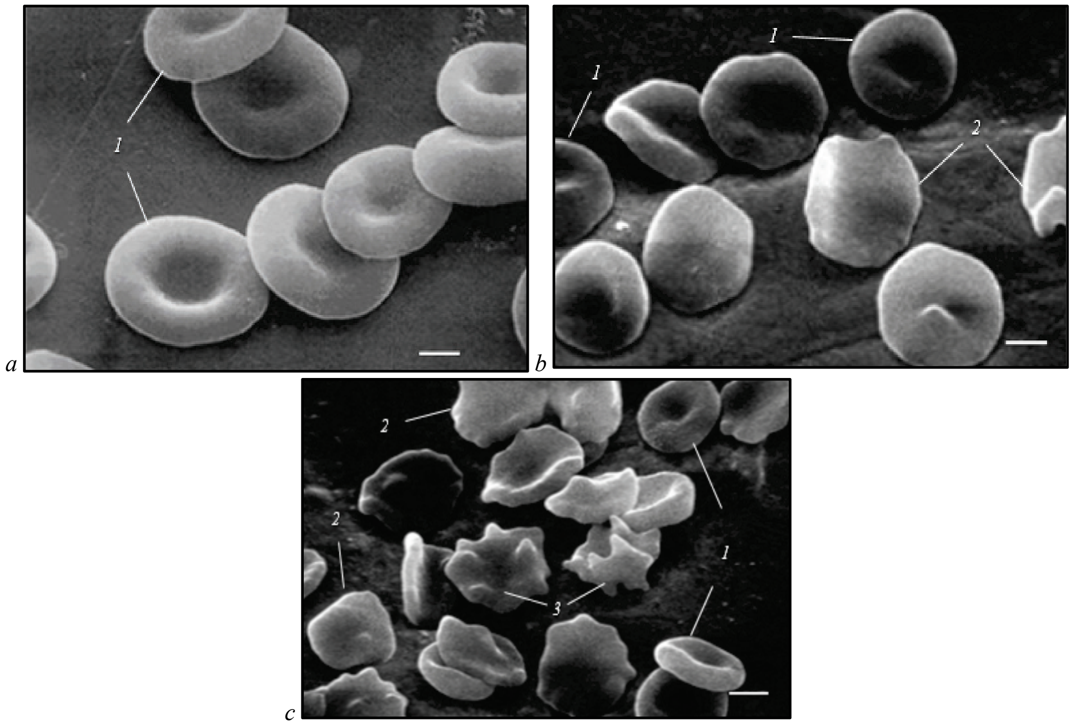

Fig. 2. General appearance of peripheral blood erythrocytes: *a* – in individuals of the control group; *b* – in patients with CRAS without vitamin D deficiency; *c* – in patients with CRAS with vitamin D deficiency: *1* – normocytes, *2* – reversibly damaged erythrocytes, *3* – acantocytes; accelerating voltage 25 kV; scale bar = 1 µm

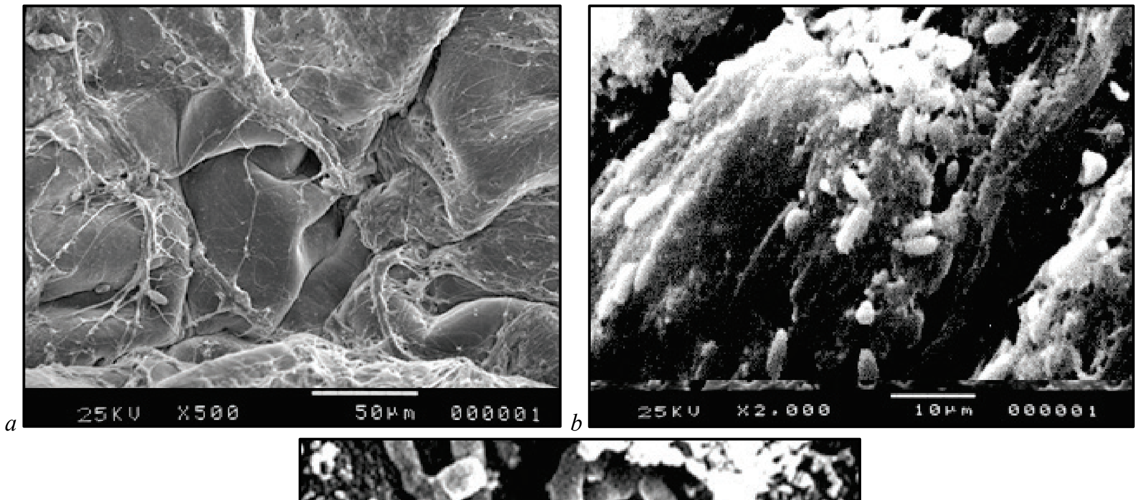

Fig. 3. General view of the surface of the oral mucosa of a patient with catarrhal gingivitis (*a*) and a patient with moderate (*b*) and severe (*c*) degree of CRAS: accelerating voltage 25 kV; scale bar: *a* – 50 µm; *b*, *c* – 10 µm

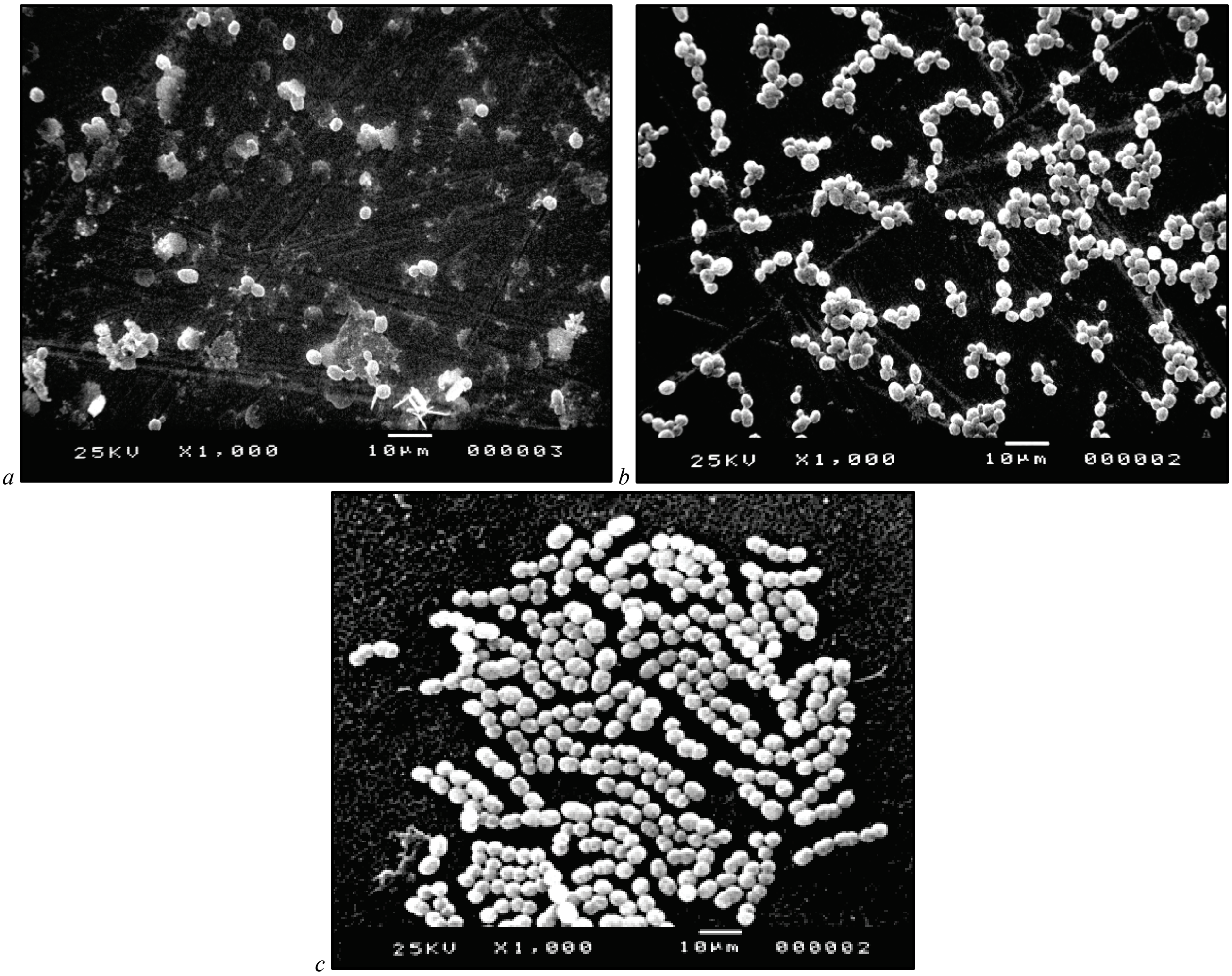

Fig. 4. The surface of the oral mucosa of patients: *a* – intact oral mucosa; *b* – predominance of coccal microflora on the surface of oral mucosa in the case of CRAS; *c* – surface of oral mucosa in the case of CRAS against the background of vitamin D deficiency; accelerating voltage 25 kV; scale bar = 10 µm

Increased colonization and increased activity of pathogenic microflora indicates a reduced activity of the immune defense system of the oral cavity in patients with CRAS, which is clearly expressed in vitamin D deficiency. Active growth of pathogenic microorganisms, in particular fungal microflora, leads to stratification of epithelial cells among themselves and increases their premature exfoliation and exposure of the underlying layer of the oral cavity epithelium. These pathophysiological processes additionally reduce local nonspecific immunity of the oral cavity, which contributes to the formation of aphthae in patients with CRAS. In turn, the elements of the lesion are subject to rapid colonization by coccal microflora, which causes local inflammation of the oral cavity and triggers a pathological cycle of pathophysiological processes characteristic of CRAS.

Discussion

Recurrent aphthous stomatitis is one of the most common diseases of the oral mucosa. Although its clinical characteristics are well defined, the exact etiology and pathogenesis of CRAS remain unclear (Porter et al., 1998). Despite detailed clinical, immunological, hematological and microbiological studies, the etiology of CRAS still remains unknown (Scully & Porter, 1989; Akintoye & Greenberg, 2005). Recurrent aphthous stomatitis is a common ulcer of idiopathic etiology, has a recurrent course, causing painful ulcers on the non-keratinized oral mucosa (Reddy et al., 2023). There are 3 clinical forms of CRAS – major, minor and herpetiform, the most common of which is minor aphthosis (Bao et al., 2018). The most common localization of CRAS is in the mucous membrane of the cheeks, tongue, floor of the mouth (Collado Pérez et al., 2023). CRAS is characterized by frequent recurrence of rashes and is accompanied by a violation of the integrity of the oral mucosa epithelium, which is manifested by a local inflammatory reaction with severe pain, which worsens the quality of life of patients (Bao et al., 2018; Rodriguez-Archilla & Brykova, 2019; Uluyol & Kilicaslan, 2019).

Recurrent aphthous stomatitis is a common chronic disease of the oral cavity, which has a large number of predisposing factors, in particular, immune changes, hematological deficiencies, oxidative stress, obesity and other environmental factors (Oluwadaisi et al., 2023). The influence of solar insolation and the role of vitamin D deficiency in the etiology of CRAS is still a matter of controversy (Safari-Faramani et al., 2024). The use of long-term empirical data from weather stations in Ukraine for the period 1900–2017 allowed us to establish and analyze significant differences in the main indicators, in particular UV radiation, the amount of precipitation in different regions of Ukraine. Thus, the annual amount of total solar radiation within Ukraine varies from 4000 MJ/m² (in the north-eastern) to 3500 MJ/m² (in the north-western regions), the annual amount of precipitation in the north-western regions of Ukraine is relatively high (650–750 mm/year) (Boychenko et al., 2016, 2018). Epidemiological data indicate a link between vitamin deficiency and dysregulation of the innate immune system (Ismailova & White, 2022).

The discovery of vitamin D receptors in many cells and organs of the body has revealed the involvement of vitamin D not only in the regulation of calcium phosphate metabolism, including the maxillofacial region, in particular, the increased incidence of dental caries, but also the involvement of vitamin D in immune processes due to its anti-inflammatory and antimicrobial effects (Al-Maweri et al., 2020; Diachkova et al., 2021). Recent studies have shown that vitamin D is a pleiotropic regulator of human physiology, playing a significant role in controlling the function of the immune system. Vitamin D was initially characterized by its role in calcium homeostasis, particularly bone metabolism, but several studies have suggested a much broader role for vitamin D in human health (Krawiecka et al., 2017). The vitamin D receptor and its enzyme (1α-hydroxylase) are present in many tissues, including macrophages, dendritic cells, and T-lymphocytes. Serum 25-hydroxyvitamin D can be converted to the hormonal 1,25-dihydroxyvitamin D in immune cells, stimulating antibacterial and antiviral responses. Studies of the mechanism of immunomodulatory effects of 25D and 1,25D have shown that vitamin D deficiency (low serum 25D levels) can lead to dysregulation of macrophage, dendritic cell, and T-cell function, with an increased risk of inflammatory diseases (Chun et al., 2014). Immunomodulatory responses to the active form of vitamin D (1,25-dihydroxyvitamin D, 1,25D) are well known, which has led to the discovery of its potential role in normal human immune function. It has become clear that macrophages and dendritic cells are able to respond to 25-hydroxyvitamin D (25D), the major circulating metabolite of vitamin D, providing a link between the function of these cells and changes in vitamin D status. In the context of pathogen infection, the presence of intracrine vitamin D is important as a key mediator of innate immune function and the role of vitamin D in the adaptive immune system to suppress inflammation and enhance immune tolerance (Schauber et al., 2007). Therefore, it follows that variations in 25D levels can affect both innate and adaptive immune responses (Fletcher et al., 2022). An important element of the innate immune response to injury is the ability, in particular, of vitamin D3 to recognize microbial invasion and stimulate the production of antimicrobial peptides and respond to them, protecting against infection (Schauber et al., 2007).

White (2012) shows how the intracrine vitamin D system of innate and adaptive immunity can be influenced by cytokine signaling pathways in immune responses to microbial infection. 1,25D, by enhancing autophagy, plays an important role in combating intracellular pathogens, especially in viral infections, which is especially important in connection with the global health crisis of 2019 caused by the coronavirus. Vitamin D deficiency is associated with increased susceptibility to viral infections, including respiratory infections, including COVID-19, so evaluating the therapeutic potential of vitamin D supplementation in infectious diseases is becoming increasingly relevant (Bishop et al., 2020).

In our study, we aimed to assess vitamin D levels in patients with chronic recurrent aphthous stomatitis and investigate the potential impact of vitamin D on its etiology. Several studies have reported a potential role for vitamin D in the development of recurrent aphthous stomatitis (Nalbantoğlu & Nalbantoğlu, 2020; Başarslan & Kaba, 2022). The authors note that vitamin D is a potent anti-inflammatory and immunomodulatory agent that can significantly affect oral homeostasis. It is believed that low levels of vitamin D, a steroid vitamin with immunomodulatory and anti-inflammatory effects, may be associated with recurrent aphthous stomatitis (Zhu et al., 2015; Zakeri et al., 2021; Oluwadaisi et al., 2023). It was found that vitamin D levels in patients with CRAS had a significant positive correlation between its levels in the serum and saliva of the patients (Bahramian et al., 2018; Uwitonze et al., 2018). It is also reported that the observed relationship between vitamin D and CRAS is probably related to the effect of the steroid vitamin on the immune system (Safari-Faramani et al., 2024).

However, there are a number of factors (including vitamin D deficiency) that lead to a decrease in the level of general and local immunity, the appearance of echinocytes in the peripheral blood, which in turn can cause increased erosion. It is known that the pathophysiology of echinocytes is such that an atmosphere enriched with Ca^{+2} ions is formed around them, which, in turn, is a trigger factor for the aggregation of discocytes (normocytes) around them and the formation of fibrin threads. These changes lead to the formation of microthrombi, respectively, certain areas of tissue are excluded from the blood circulation, on which elements of the lesion may subsequently appear. It has been reported that CRAS is a multifactorial T-cell mediated disease with immune dysregulation (Chiang et al., 2019). Factors that alter immunological responses in CRAS include vitamin and micronutrient deficiencies, including anemia, serum iron, vitamin B_{12}, and folate deficiency. Hematite and iron deficiencies may be a possible precipitating factor in CRAS recurrence, as they are twice as common in patients with CRAS than vitamin D deficiency (Rodriguez-Archilla & Brykova, 2019). Ferritin or vitamin D deficiencies may be causative of CRAS, and their determination may aid in diagnosis (Koparal et al., 2023). Significant variations in hematite deficiencies have been demonstrated in CRAS patients of different sexes and ages (Bao et al., 2018).

Iron is an important element of the body, which is involved in many physiological processes, most of which is found in red blood cells in the form of hemoglobin. Iron deficiency is the most common nutrient deficiency worldwide, although it is not considered a disease, but only a symptom of the underlying disease (Brunner & Wuillemin. 2010; Płudowski et al., 2023). In patients with CRAS, the most common systemic disease in the studies conducted, in addition to hypertension and allergies, was anemia, the potential role of which is considered as a modifier of the immune response at CRAS (Koybasi et al., 2006; Ślebioda & Dorocka-Bobkowska, 2019). The causes of iron deficiency anemia include increased iron requirements, insufficient dietary intake, and disorders affecting its absorption. Under certain circumstances, iron deficiency anemia can contribute to atrophic gastritis, either autoimmune or caused by *Helicobacter pylori* infection (DeLoughery, 2017).

It is known that one of the key elements of the microcirculation are erythrocytes, which are able to pass through capillaries and deliver oxygen to cells due to high degrees of deformability associated with the characteristics of the erythrocyte membrane. Changes in erythrocyte deformability as a result of membrane damage, partly related to increased synthesis of reactive oxygen species, can be observed in various pathological conditions, leading to changes in the microcirculation (Steenebruggen et al., 2023). The state of erythrocyte oxygenation regulates, as functional studies have shown, many important pathways, including glucose metabolism, mechanical membrane stability and the release of cellular adenosine triphosphate (Chu et al., 2016). Due to substitutions or deletions of amino acids that change the normal tertiary structure of hemoglobin, unstable disorders occur, which lead to increased oxidation to methemoglobin and loss of heme. This results in heme denaturation and precipitation, associated with severe oxidative membrane damage and destabilization of cytoskeletal protein interactions and increased permeability to potassium ions (Ideguchi, 1999). As hemoglobin begins to denature, it forms hemichromes that bind to the core protein spanning the erythrocyte membrane, enabling recognition by antibodies that bind to old erythrocytes and cause their removal from the circulation (Low, 1991). Damaged erythrocytes are phagocytosed by macrophages, resulting in hemolysis. This hypothesis is based on immunological findings and is consistent with many of the features of unstable hemoglobin (Ideguchi, 1999). Under the influence of external stimulation, erythrocytes undergo metabolic and structural changes, one of which is the redistribution of hemoglobin between the cytosol and the cell membrane, to which a part of hemoglobin can be attached, which can affect the mechanical properties of the cell and the ability to deform (Barshtein et al., 2024; Kawabata, 2024). The deformability of erythrocytes is important for microcirculation in the body, as it can be defined as the ability of the cell to change shape in response to an external force. The ability to deform erythrocytes can be regulated by Ca^{+2}/protein kinase C signaling mechanisms through phosphorylation changes in erythrocyte membrane proteins. Improving the mechanical properties of erythrocytes, reducing their shear-induced deformability, through the Ca^{+2}/protein kinase C signaling mechanism can facilitate the flow of erythrocytes into the microcirculation in pathophysiological disorders (Ugurel et al., 2021).

Assessment of erythrocyte deformability under hypoxia and modeling of erythrocyte dynamics in the bloodstream can be used to determine hypoxia-mediated changes in erythrocyte deformation to monitor blood flow in hypoxic tissues (Ugurel et al., 2020). The concept of active regulation of erythrocyte deformability is known, which is mainly associated with altered associations between membrane skeletal proteins and integral proteins that serve to attach the skeleton to the lipid matrix. Red blood cell deformability is determined by the geometric properties of these cells, where shear stress induces changes in the deformability of red blood cells at physiologically relevant levels. Improving red blood cell deformability by shear forces may have a significant impact on blood flow dynamics in tissues supplied by blood vessels with impaired vasomotor reserve and serve as a compensatory mechanism to maintain adequate microcirculation (Meram et al., 2013). Red blood cell deformations that promote vesicle formation may be caused by an adapted oscillatory shear flow. Such oscillatory shear flow provides an ideal environment for a wide range of representative biochemical effects associated with metabolic disorders (Asaro et al., 2018). Our study indicates a significant association between repeated episodes of CRAS and low serum vitamin D levels in patients. Further well-designed studies are needed to clarify the role of vitamin D in the pathogenesis of recurrent aphthous stomatitis (Al-Maweri et al., 2020).

In our study, we demonstrate an association between low vitamin D levels and the development of recurrent aphthous stomatitis and its course. We have demonstrated an association between vitamin D levels and oral mucosal diseases, including CRAS, which will help clinicians reduce the risk of recurrence and ensure favorable treatment outcomes through knowledge and timely laboratory testing. Since CRAS is an immunologically mediated disease, local and systemic therapy should consider etiological factors when choosing CRAS treatment methods. Studies that have identified a potential association between low serum vitamin D levels in patients with CRAS, supporting a role for vitamin D in the pathogenesis of the disease, suggest the potential for vitamin D supplementation in the treatment of CRAS patients (Al-Maweri et al., 2023). Vitamin D_3 supplementation can increase serum $25(OH)D_3$ concentrations and, consequently, antimicrobial activity (Vargas Buonfiglio et al., 2017).

Conclusions

As our study showed, with relapse of CRAS in patients with vitamin D deficiency or insufficiency, the morphological characteristics of erythrocytes are modified. In this case, peripheral blood erythrocytes undergo structural and functional transformations, the pathogenetic basis of which is the flicker-resonance increase in the amplitude and frequency of oscillations of the oscillating fluid of membranes and cells as a whole. High-frequency shift due to an increase in body temperature in the acute phase of CRAS enhances the melting of lipids and increases the fluidity of membranes, as a result of which the discs are stretched and thinned, the central pits deepen and the roughness decreases, the volume and number of cone-shaped pores increase, as well as the density of erythrocytes. Such changes in the structure and physical and mechanical properties initiate apoptosis and enhance aggregation interactions, resulting in risks due to the destruction of cell membrane surfaces, increased aggregation interactions and activation of apoptosis. These changes lead to the formation of microthrombi, and accordingly, a certain area of tissue is excluded from the blood circulation, which, against the background of a decrease in the level of immunity, leads to increased erosion of the oral mucosa and causes the development of local manifestations of CRAS. Our studies of the dependence of epithelial insufficiency on vitamin D deficiency and the assessment of the potential protective and therapeutic role of vitamin D in recurrent aphthous stomatitis will allow us to develop and implement in clinical practice new approaches to the treatment of patients using etiopathogenetic therapy.

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