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ABSTRACT

of the dissertation for the degree of Doctor of Sciences

SUBSTANTIATION OF COMPLEX APPROACHES TO DENTAL CARE FOR PATIENTS WITH β-THALASSEMIA

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GENERAL REVIEW OF THE WORK

Relevance of the topic. Thalassemia is one of the most common genetic diseases in the group of blood pathologies.

The World Health Organization (WHO) reports about 300 thousand patients with various forms of thalassemia and about 250 million carriers worldwide[1].

Particular attention is paid to the homozygous form of beta thalassemia (beta thalassemia major), which is characterized by the most severe clinical symptoms, due to a genetic defect in the synthesis of the beta-chain of hemoglobin.

In case of illness, excessive destruction of red blood cells leads to anemia and severe life–threatening metabolic disorders.

β-thalassemia is most common in the countries of the Middle and Far East, India, Southwest Asia, Turkey, Iran, Greece, Cyprus, Southern Italy and Southern Spain. These zones are called the "thalassemic belt"[2,3,4,5].

In Azerbaijan, β-thalassemia, occurs in 8-15% of the population depending on the region and 200-300 children are born with this disease every year[6].

According to incomplete estimated demographic data, there are currently over 4,000 patients with the homozygous form and more

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[6] Юсифова А. А., Алекберова С. А., Асадова Б. Г. Статистические показатели пациентов с большой и промежуточной β-талассемией в разных регионах Азербайджана // Бюллетень науки и практики, – 2020. №11,– с. 242-247

than 500,000 carriers of vicious genes in Azerbaijan, which determines the enormous medical and social significance of this disease for the state[7,8,9,10].

Over the past 10 years, unprecedented measures have been taken at the state level in order to combat and to prevent thalassemia in Azerbaijan[11]. Significant reforms and a number of projects aimed at treating and diagnosing this disease have been implemented in the Republic.

Thus, the law "On state care for patients with hereditary blood diseases - hemophilia and thalassemia AR", adopted by the parliament of the country, is being successfully implemented with the personal assistance of the President of the Republic of Azerbaijan, Ilham Aliyev.

Currently, it has been possible to significantly prolong the life of patients suffering from severe manifestations of β-thalassemia major due to government measures and efforts of specialists.

This is facilitated, first, by the "Thalassemia Center" founded by the First Vice-President of the Republic of Azerbaijan, Mehriban Aliyeva, within the framework of the Heydar Aliyev Foundation's program "For life without thalassemia". The implementation of this

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[9] Акперова, Г. История изучения и решения проблемы β–талассемии в Азербайджане // Клиническая медиина Казахстана– 2013– №4 (30), – с. 21-28

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program is one of the priority areas of the foundation's activity for the protection of children's health.

To compensate for the congenital hemoglobin deficiency, patients with β-thalassemia major require regular blood transfusions, which aggravates the accumulation of iron in the body and the development of hemosiderosis of organs and tissues.

This is a process of additional impairment and risky for the life of patients, causing damage to the endocrine glands and multifactorial endocrine insufficiency; heart failure and risks of its dysfunction; severe immunosuppression, leading to failure of the body's anti-infectious defense and the work of signaling systems[12,13,14,15].

The mechanisms programmed by the initial congenital hematological pathology and its treatment methods have a pathogenetic significance in the development of dental morbidity.

Dental pathology in β-thalassemia major, as a rule, has a widespread generalized character with elements of inflammation and degenerative tissue modification, significantly contributing to the initiation and maintenance of systemic inflammatory response mechanisms in the body.

The most common nosological condition, such as dental caries, inflammatory diseases of periodontal tissues (with or without damage to the gingival junction), chronic foci of odontogenic

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infection are characterized by considerably earlier development and multiple lesions[16,17,18,19].

However, the use of traditional approaches to treatment is not sufficiently effective, as a result of which an acute disease becomes chronic and spreads, is not sufficiently effective.

Recurrent microbial inflammation in the oral cavity triggers cytokine cascades that initiate cellular apoptosis, which can target any organ[20,21,22].

This means that dental pathology due to β-thalassemia major may play a trigger role in unfavorable prognosis.

Consequently, some of these features determine the relevance and medico-social significance of this study.

To solve the urgent modern medico-social problem of prolonging the life of β-thalassemia patients, an integrated interdisciplinary approach is necessary to assess their potential

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viability. This requires a change in the prevailing attitude towards dental diseases as local pathology of the oral cavity [23, 24].

The pathogenetic interrelation of associated diseases in polymorbid complexes of β-thalassemia major patients has not yet been studied. Age- related characteristics of dental status have not been determined. There is a gap in literature data on the role of dental pathology within the general somatic mechanisms that form the mortality risk and identify these patients' survival rate.

Despite the numerous works devoted to the description of the "thalassemic physiognomy" of patient with β-thalassemia, the place of orthodontic correction in the complex of therapeutic and prophylactic measures has not been determined yet, the anthropometric characteristics of the maxillofacial region remain unsystematized, and its morphological features at the cellular and molecular level have not been sufficiently studied.

The totality of white spots in modern concepts of β-thalassemia major determine the relevance of a comprehensive study aimed at the formation of the concept of the thalassemic continuum, which will allow to define the place of dental pathology as a cluster of polymorbidity and form algorithms for interdisciplinary supervision of patients with β-thalassemia major.

Object of the study. The study included patients with β-thalassemia major, dental patients without somatic pathology.

The aim of this study: To determine dental status features of modern patients with β-thalassemia major for increasing the efficiency of their supervision.

Research objectives:

1. Study of age-related characteristics of the structure of dental morbidity in patients with β-thalassemia major.

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2. Study of the features of craniofacial changes in patients with β-thalassemia major.
3. Assessing the histological picture of the periodontal tissue cellular - molecular modifications in patients with β-thalassemia major.
4. Study of vital macro - and microelements in the metabolism features of dental patients with β-thalassemia major.
5. Determing the inflammatory factors' activity in dental patients with β-thalassemia major.
6. Development of integrated approaches to the prevention and treatment of oral cavity diseases in patients with β-thalassemia major.
7. Evaluation of treatment efficiency with the use of a complex preparation of natural origin for inflammatory periodontal diseases in patients with β-thalassemia major.

Research methods. The studies were carried out using modern complex methods, including clinical, morphological, laboratory, microbiological, radiological, photometric and biometric, statistical studies.

The main provisions for the defense:

1. A high level of dental morbidity in patients with β-thalassemia major is associated with severe craniofacial deformities and homeostatic disorders caused by hereditary hematological diseases in the organism.
2. In the structure of dental diseases in adult patients with β-thalassemia major, carious lesions of the teeth, inflammatory periodontal diseases and chronic foci of odontogenic infection prevail.
3. Pathogenetically significant for the development of dentoalveolar pathology in adult patients with β-thalassemia major are mineral imbalance, initiation of cytokine cascades of systemic inflammatory mechanisms, metabolic immuno-suppression caused by hemosiderosis of immune cells.
4. There is a correlation between the ultrastructural parameters of the cellular structure's congestion with iron-containing

elements and the development stages in chronic sclerotic process of the periodontal tissues.

5. Patients with β-thalassemia major require systematic metabolic correction as an integral part of the therapeutic and prophylactic measures to prevent dental diseases and increase their treatment efficiency.
6. By establishing the correct tuberous-fissure contacts and eliminating occlusal overload, orthodontic correction of patients with β-thalassemia major contributes to the prevention of inflammatory periodontal diseases, which contributes to the prevention of dental morbidity.

Scientific novelty of the research.

For the first time on the basis of modern complex research methods:

1. An integrative approach was applied to the study of dental pathology in patients with β-thalassemia major, taking into account the regular manifestations of general somatic homeostatic disorders caused by a hereditary disease in the oral cavity.
2. Nosological priorities of dental morbidity in different age groups, reflecting the development of metabolic disorders in patient's organism, were established.
3. Data on the most pronounced orthodontic disorders in the contingent of growing children versus adult patients were presented.
4. Original data on the quantitative characteristics of craniofacial deformities developing in β-thalassemia major as an additional patagnomonic diagnostic sign were presented.
5. Histological and electron-microscopic characteristics of the structural rearrangements of the periodontal tissues cellular and fibrillar structures at various stages of the chronic gingivitis in patients with β-thalassemia major have been studied in detail.
6. New data on the ultrastructural parameters of the ferritin molecules and accumulations of siderosomes and hemosiderin in the periodontal tissues are presented.

7. The biochemical substrates of the pathogenetic relationships of dental diseases with general somatic status disorders, caused by a hereditary disease have been studied. The impact of metabolic changes, including macro and microelements metabolic disturbances, cytokine imbalance, a consequence of hemosiderosis of organs and tissues, as well as the oral cavity, have been identified.
8. The points that require the application of alternative approaches to increase dental care efficiency in patients with β-thalassemia major were identified. These are: the need to correct mineral metabolism disorders, maintenance of cytokine balance, the importance of immunorehabilitation.
9. A remedy based on oil extracts of medicinal plants for the treatment and prevention of periodontal and oral mucosal diseases was developed. (Eurasian patent No. 036150 dated 05.10.2020).

The practical significance of the obtained results.

The significant applied value of the conducted dissertation research is:

1. The development of a concept of dental pathology as a cluster of the polymorbid continuum in patients with β-thalassemia major.
2. The establishment of the nosological priorities of stomatological morbidity in different age groups of patients with β-thalassemia major;
3. Specification and systematization of quantitative parameters of craniofacial deformities as an anthropometric basis for the recognition of pathognomonic symptoms in β-thalassemia major;
4. The development of a program for systematic additional examination of patients with β-thalassemia major in the course of their dispensary observation;
5. The application of a biological preparation based on medicinal herbs for the prevention of inflammatory periodontal diseases;
6. Methods of orthodontic correction in patients with β-thalassemia major contributes to the improvement of their

quality of life, which justifies the introduction of orthodontic service in the organization of dispensary dental care for these patients.

Approbation of work. The research results were reported at: XIX-International Conference of Maxillofacial Surgeons and Dentists "New Technologies in Dentistry", St. Petersburg, Russia, 2014; XX-international conference of m/f surgeons and dentists, St. Petersburg, Russia, 2015; V-th All-Ukrainian Scientific Conference "Physiology - Medicine, Pharmacy and Pedagogy: Actual Problems and Modern Achievements", Kharkov, 2018; 24th International Conference of Maxillofacial Surgeons, Rio de Janeiro, Brazil, 2019; 1st Azerbaijan International Congress of Hematology Specialists, Baku, 2019; International scientific and practical conference dedicated to the 100th anniversary of the Faculty of Medicine, Baku, 2019; XX Anniversary Congress of Orthodontists of Russia, Sochi, Russia, 2019; 95th Congress of the European Orthodontic Society, Nice, France, 2019; International conference dedicated to the 100th anniversary of the Department of Human Anatomy of the Azerbaijan Medical University, Baku, 2019; IX International Orthodontic Congress, Tokyo 2020; VI International Medical and Health Research Congress - UTSAK Ankara 2021.

The materials of the dissertation were discussed at a joint meeting of the departments of dentistry, orthopedic, surgical, therapeutic, pediatric dentistry and human anatomy and medical terminology of the AMU (protocol No. 1 from 7.04.2021); at the scientific seminar of the Approbation Commission at the Dissertation Council ED.2.05 AMU (protocol No.6 dated 27.05.2021).

The name of the organization where the dissertation has been carried out. The work was performed at the Department of Dentistry (until 2018), Pediatric Somatology, Microbiology and Immunology, Pharmaceutical Technology and Management, the Educational and Clinical Laboratory of Biochemistry, the Research Center of the Electron Microscopy Laboratory of the AMU, the Republican Center of Thalassemia.

Implementation of research results into practice.

The research results are being implemented in the educational process at the Pediatric Dentistry Department of the Azerbaijan Medical University (AMU), into the practical work of the Dental Clinic of the AMU, and, as well as in the Thalassemia center in Baku.

Publications. On the topic of the dissertation work, 65 works have been published, including 31 articles (24 of them abroad, 7 - local), 27 publications in collections of scientific and practical conferences, 5 thesis, 1 monograph and 1 patent for an invention has been received.

The structure and volume of the dissertation. The dissertation consists of the following chapters: introduction (15009 characters), literature review (66572 characters), chapters describing materials and research methods (38026 characters), 5 chapters (134589 characters), conclusions (80843 characters), outcomes (3491 characters), practical recommendations (1166 characters), a list of literature findings (44 page), annexes (8 pages). The work is presented on 332 pages (339696 characters) of computer text, contains 36 tables, 7 charts and 59 figures. The bibliographic index includes 381 works.

MATERIAL AND RESEARCH METHODS

To achieve the goal of the study, a number of successive stages united logically substantiating complex general somatic approaches to the prevention and improvement of the dental care efficiency in patients with β-thalassemia major (BTM) have been performed.

Stage I - the study of age-related characteristics of dental morbidity in patients with BTM, identifying the nosological priorities that form in patients in adulthood.

Stage II – the study of the features of the dental status in patients with BTM, determining the specific anthropometric, histological, and metabolic characteristics of homeostasis.

Stage III - determining the application directions and points of pathogenetic correction for the prevention and improvement of the

dental care efficiency in conditions of the polymorbid continuum in BTM patients.

Stage IV - study of the efficiency and safety of using a complex neutral preparation of natural origin to provide a multimodal corrective metabolic action in the treatment of inflammatory periodontal diseases in BTM patients. Assessment of the contribution of orthodontic treatment to the improvement of the dental and general somatic status of patients with BTM.

The study involved a total of 321 patients with BTM at the ages of:

- 3 to 5 years - 59 people (18.4%), I observation group.
- 6 to 12 years - 140 people (43.6%), II observation group.
- 13 to 17 years - 57 people (17.8%), III observation group;
- 18 and more - 65 people (20.2%), IV observation group.

The control group included 382 dental patients without established somatic pathology. They were divided into similar age groups corresponding to the stages of occlusion formation: temporary, interchangeable, early permanent.

Control observation group I included 33 children (8.6%); the II group - 179 children (46.9%); the III control observation group - 85 adolescents (22.3%); the IV group included 85 people (22.3%).

The biochemical laboratory research was carried out in the clinical and biochemical laboratory of the Azerbaijan Medical University. Taking into account the age-specific versatility of range norms for the studied parameters, as well as a slight difference in the obtained values of laboratory findings, the control group was not divided into age subgroups. All involved in the study BTM patients received adequate blood transfusion replacement and chelation therapy (desferal).

Clinical examination and assessment of the dental status of patients were carried out in accordance with the recommendations of the WHO, 1997.

The assessment of the oral cavity hygienic state was carried out according to indices (U.A. Fedorov and V.V. Volodkina (DMFT); Green-Vermillion index (OHI-S); Silness-Loe, (Podshadley, Haby, 1968) index of plaque).

For an objective assessment of the state of periodontal tissues during the observation and treatment of patients, the following clinical tests were used: papillary-marginal-alveolar index (PMA, Parma C., 1960); the degree of gum bleeding (Muhlemann H.R., Cowell I., 1975); CPITN index (Community Periodontal Index of Treatment Needs, 1980); gingivitis index Gingival Index (GI) - (Loe & Silness, 1963). The intensity of dental caries was determined by the KPU index (WHO, 1962).

Orthopantomography (OPTG), direct and lateral teleroentgenograms (TRG) of the head were performed by a Morita Veraview X-ray apparatus (Japan) using a standard technique.

The study of lateral TRGs to identify characteristic changes in patients with thalassemia was carried out using the computer software "Dolphin - Imaging 11.9" using "Ricketts, McNamara, Steiner (Tweed), Jarabak, McLaughlin, Bjork, Quas / Airway analysis". Patient photographs were also evaluated in this program. Biometric measurements on diagnostic models of the jaws were carried out by hand, as well as by scanning the patient's teeth and obtaining digital models in stl format, which were processed by the Romexis computer program of the Finnish company Planmeca.

In order to optimize the dental examination and describe the condition of the dentition of the surveyed contingent, a diagnostic dental card was developed. The patient's personal data, the research findings and medico-prophylactic measures were included in the computer database.

Laboratory research methods

The state of the microbiocenosis of the oral cavity was assessed according to the data obtained from one of the main biotopes of the oral cavity - mixed oral fluid. Daily cultures of microorganisms isolated from the mixed oral fluid at a dilution of 1: 1000 were plated on Petri dishes with selective nutrient media - blood agar, yolk-salt agar, Sabouraud's medium.

To determine the ultrastructural features of the gingival tissue elements structure, the method of electron microscopic examination was used.

Material processing - fixation, postfixation, dehydration and pouring into Araldite-Eponovye blocks was carried out according to the generally accepted method.

From these blocks, sequentially cut, stained by trichromic staining according to F. D'Amico (2005) and unstained ultrathin sections with a thickness of 35-70 nm were prepared for examination on a transmission electron microscope JEM 1400 (JEOL-Japan) using a Leica EM UC7 ultratome.

Photographing and obtaining morphometric indications of the gingival structural elements were done using a side digital camera Veleta and software iTEM.

Iron metabolism was determined by indications of serum iron (SI); total iron binding capacity of serum (TIBC), latent iron-binding capacity of blood serum (LIBC), saturation percent of transferrin with iron (% STI), serum ferritin, serum hepcidin were revealed by colorimetric method using NitroPAPS as chromogen.

Ferritin was determined using a set from “Pishtaz Teb diagnostic” (Iran), hepcidin was determined using tests from “Cloud-Clone Corp” (USA).

When determining the level of calcium, phosphorus, as well as the activity of alkaline phosphatase in the blood serum, photometric methods were used on a “STAT FAX 1304 plus” biochemical analyzer (USA), using commercial reagent sets from “Human” (Germany).

To determine the concentration level of IL-2, IL-6, IL-10, TNF-α, TNF-α in the blood, the method of enzyme-linked immunosorbent assay (ELISA) was used by a set of reagents "Vector BEST" (Russian Federation). The results were presented on a StatFax 303 + strip immunoassay analyzer at a wavelength of 450 mm (differential filter 650 mm).

Methods for statistical processing of digital data. The obtained digital data were subjected to statistical processing by methods of variational (W-Wilkokson, KU-Kruskal-Wallis), correlative (ρ-Spearman) and discriminant (Chi-Square) analyses on the EXCEL-2010 and SPSS-20 spreadsheet.

RESEARCH RESULTS AND DISCUSSION

Results of the study of dental pathology in patients with β-thalassemia major.

A distinctive clinical feature of BTM patients was a high general somatic morbidity with early formation of polymorbid status.

From an early age, a pronounced tendency towards an increasing burden of the general somatic background with chronic inflammatory foci and diseases (chronic bronchitis, chronic Pyelonephritis, chronic foci of infection of different localization, generalized periodontitis and gingivitis, myocardial dystrophy, etc.) was established. The 100% infection rate of homozygous older patients with herpes viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex) was of special attention. Moreover, the unconditional aggravating factor leading to polymorbidity in homozygous patients is the inevitable hemosiderosis of internal organs. This fact was observed in 42.8% of patients in the younger age group, in 43.5% of children aged 6-12 years and, in all patients, over 13 years old.

Clinical examination of patients with BTM revealed pallor of the skin with a yellowish or earthy tint. Icterus (color in yellow shades) of the outer albuminous membranes of the eyes was observed. The jaundiced skin color was the result of the deposition of excess bile pigment in the skin, formed by hemolysis of abnormal red blood cells. There was a noticeable increase in the outlines of the boundaries of the abdominal cavity due to the enlargement of the liver and spleen. The patients were characterized by a retardation in physical and sexual development, general malaise, increased fatigue, and decreased immunity. Pale (bloodless) and atrophic structures of the oral mucosa were characteristic signs of the clinical state of the oral cavity organs and tissues in patients with BTM.

Examination of the mucous membranes of the cheeks revealed their yellowish tint, thinning and loss of elasticity. Patients complained about damage to the epithelial covers of the cheeks and corners of the mouth, which required long-term specific treatment. Atrophy of the epithelial cover, edema, small cracks were also

observed on the tissues of the tongue. Atrophic oral mucosa, accompanied by xerostomia, led to the fact that patients suffered from unpleasant sensations of taste while eating and bad breath.

The most common diseases of the mucous membranes were cheilitis. In most cases, the exudative form of exfoliative cheilitis prevailed. On the background of edema and a cyanotic red border of the lips, more often in the corners of the lips, scales or crusts of a dirty yellowish or brown color were formed associated with microbial infection. The frequent cases of eczematous cheilitis and chronic lip fissures with little discharge, tenderness and long epithelization should also be pointed out.

Changes in all structures of the gingival complex were found in the periodontal tissues. The color of the gums depended on the degree of anemia. With a sharp decrease in hemoglobin level, the gum became pale with loss of vascular pattern and acquired a dark color due to ferritin increase in the blood, because of hemosiderosis associated with therapeutic transfusion therapy. Thus, we observed a variety of shades in the gingival tissue color – from pronounced moderate hyperemia and cyanosis to pallor of the mucous membranes, slight detachment of the gingival papillae, exposure of the teeth roots with the deposition of yellow-brown non-mineralized or mineralized rust–like plaque, difficult to remove when scraping.

The study compared the structure of dental morbidity in different age groups in patients with BTM (main observation group) and in dental patients without somatic pathology of the corresponding age (control observation group).

It was found that, starting from a young age, the incidence of dental diseases in hematological patients significantly exceeded the frequency in the control group.

When analyzing the hygienic state of the oral cavity according to Fedorov-Volodkina, no statistically significant differences in the younger age group (3-5 years old) were revealed. In the control group, the index was 2.19 ± 0.09 versus 2.25 ± 0.05 in the main group, which indicates unsatisfactory oral hygiene in both groups of the examined.

When assessing the level of oral hygiene in the age group of 6-12 years, a significant increase in the index for the group of examined patients with BTM ($p < 0.001$) was found.

In the main group, it was 2.98 ± 0.07, and in the control group, 2.56 ± 0.07 points ($x2 = 15.23$; $p < 0.01$). Meanwhile, if a satisfactory oral hygiene index was observed in $12.8 \pm 2.5\%$, an unsatisfactory index in $41.3 \pm 3.7\%$, and poor hygiene in $45.3 \pm 3.7\%$ for the subjects in the control group, then in the main group, these indicators were $4.3 \pm 1.7\%$, $30.7 \pm 3.9\%$, and $65.0 \pm 4.0\%$, respectively.

Comparing the average indicators of oral hygiene in patients with BTM and somatically healthy individuals in the third age group (13-18 years), a significant increase in the OHI-S index by 1.9 times ($p < 0.001$) was revealed. In the main group, the index value was 3.11 ± 0.15 points, and in the control group 1.62 ± 0.09 points ($x2 = 65.16$; $p < 0.001$). At the same time, satisfactory hygiene in the control group was observed in $54.1 \pm 5.4\%$, and in the main group only in $10.5 \pm 4.1\%$ of the surveyed. Unsatisfactory oral hygiene in the control group was in $35.3 \pm 5.2\%$ versus $24.6 \pm 2.4\%$ in the main occlusal overload group ($x2 = 65.16$; $p < 0.001$). In $64.9 \pm 6.3\%$ in the first group occlusal overload, and only in $4.7 \pm 2.3\%$ of cases in the second group, «poor hygiene» index criterion was noted.

The OHI-S hygiene index in the main fourth age group (≥18 years) was 3.60 ± 0.11 points, and in the control group, 2.13 ± 0.10 points ($x2 = 53.72$; $p < 0.001$). When interpreting the index values, it was found that only 2 patients among 65 of the main group ($3.1 \pm 2.1\%$) had satisfactory and 5 people ($7.7 \pm 3.3\%$) had unsatisfactory indicators, and in the remaining 58 patients ($89, 2 \pm 3.8\%$), poor oral hygiene was noted. In the control group, a satisfactory hygiene index was in $32.9 \pm 5.1\%$ of cases, unsatisfactory hygiene in $36.5 \pm 5.2\%$ and poor hygiene in $29.4 \pm 4.9\%$ of cases, which is 2.3 times less than in somatically healthy individuals The data obtained indicate a deterioration in oral hygiene in all main groups.

The study of the age-related dynamics of oral hygiene showed that a more favorable situation was found in somatically healthy individuals. In the group of BTM patients, there is a decrease in the level of individual oral hygiene with age.

The work studied the prevalence and intensity of inflammatory periodontal diseases in patients with BTM.

Thus, the PMA and bleeding index in thalassemic patients exceeded the levels of these indicators in somatically healthy individuals, starting from the first age group and growing to a maximum in the fourth age groups of observation ($p < 0.001$). The average value of the PMA index in the second main age group was $35.67 \pm 0.5\%$ versus $22.61 \pm 0.70\%$ in the control group, which indicated a more pronounced inflammatory process in the periodontal tissues in BTM.

The main complaints of children were bleeding and soreness of the mucous tissues of the gums when brushing their teeth. Unjustified refusal to brush the teeth contributed to the accumulation of plaque and deterioration of the hygienic state of the oral cavity, which led to inflammation, hyperemia and swelling of the interdental papillae and the marginal part of the gums. High index values in this age group are also associated with the period of tooth replacement.

In the third and fourth main age groups, there was an increase in the digital values of the PMA index and a significant difference from the control age group of 13-17 years was 37.35 ± 1.09, which was two times higher than the values of the control group ($p < 0.001$). In patients of the age group above 18 years, up to $41.09 \pm 1.03\%$ versus $26.59 \pm 1.12\%$ ($p < 0.001$), which indicates a gradual increase in chronic gingival inflammation with age.

Also, in patients with BTM in the third age group, $21.1\% \pm 5.4$ patients had a mild degree and $78.9 \pm 5.4\%$ of patients had an average degree of inflammation. In the fourth age group, $10.8 \pm 3.8\%$ of patients with BTM had a mild degree of inflammation, $86.2 \pm 4.3\%$ had a moderate degree, and $3.1 \pm 2.1\%$ had a severe degree of inflammation. The older the patient's age and the severity of the underlying disease, the more severe the signs of periodontal damage were.

When analyzing the table of results of the study of the index of bleeding (CI) according to Müllemann, the fact of the dependence of the degree of bleeding on the age of the patient also attracted attention.

In a comparative analysis of the bleeding index findings in patients aged 6-12 years, it was revealed that a mild degree of inflammation was observed in 14.4% ± 3.0 of the main group and in 46.8% ± 4.0 of the control group patients.

The average degree of inflammation is present in 52.5% ± 4.2 of the main group and in 46.8 ± 4.0% of the control group patients. Study revealed severe bleeding in the main and control groups, respectively, in 33.1% ± 4.0 and 6.3% ± 1.9 of patients.

A mild degree of inflammation was detected in the main age group of 13-17 years in 1.8 ± 1.8% of BTM patients and in 63.4 ± 5.3% of the control group dental patients. The average degree of inflammation in 25.0 ± 5.84% of cases in the main and in 35.4 ± 5.3% - in the control, severe in 73.2 ± 5.9% of cases in the main and 4.3 ± 2.9% - in the control group were noted.

In the main group of the adult BTM patient contingent (≥18 years old), a mild degree of inflammation in 1.5 ± 1.5%, an average degree in 26.2 ± 5.5%, and a severe degree in 72.3 ± 5.6% of the cases were noted.

In the control group of the same age contingent, a mild degree of inflammation in 32.9 ± 5.1%, an average degree of inflammation in 43.5 ± 5.4%, and a severe degree of inflammation in 23.5 ± 4.6% of the patients were noted.

When evaluating the criteria of the CPITN index, it was found that 82.2 ± 3.3% of patients in the main group at the age of 6-12 years need to improve oral hygiene, which corresponds to code 1.

17.8 ± 3.3% of patients need to improve individual and professional oral hygiene, which corresponds to code 2.

In the age group of 13-17 years, code 1 was found in 36.4 ± 6.5%, code 2 - in 50.9 ± 6.7%, and 12.7 ± 4.5% of patients need professional oral hygiene and curettage, which corresponds to code 3. In the adult group ≥18 years, code 1 was observed in 3.1 ± 2.1% of the examined, code 2 - in 33.8 ± 5.9 % of the examined, and a sign of periodontal lesion (the value of the index code –3) was found in 61.5 ± 6.0% of the patients. One patient (1.5 ± 1.5%) had a pocket up to 6 mm, which corresponds to the highest value of the CPITN index and requires complex treatment of periodontal diseases.

The study of indicators of periodontal lesions intensity signs showed that the degree of inflammatory periodontal diseases in the main groups was increasing with age.

The average number of healthy periodontal sextants in BTM patients aged 6-12 years was 2.70 ± 0.14, in the age group of 13-17 years it was 1.45 ± 0.22, and 1.00 ± 0.15 in the group over 18 years. In the somatically healthy group, the number of intact sextants was 3.10 ± 0.12, 3.23 ± 0.23, 2.73 ± 0.18, respectively, in the age groups (chart 1).

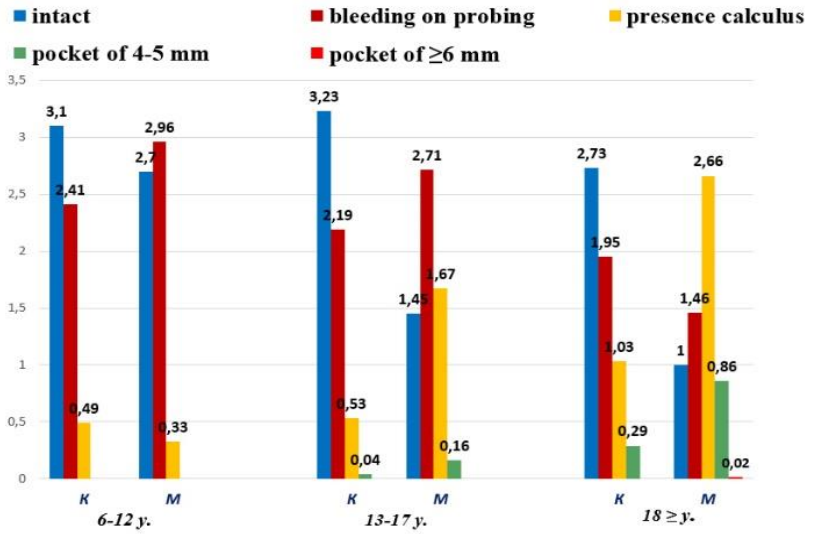

Chart 1. Intensity indicators of periodontal pathology signs in patients of the control and main groups

At the same time, the highest rate of caries prevalence was observed during the period of temporary occlusion and amounted to 93.9 ± 4.2%, and with age there was a tendency to a decrease in the prevalence of caries of both temporary and permanent teeth. However, in patients with BTM, this indicator was 100% in all age groups.

The average values of the intensity of dental carious lesions varied depending on the age of the examined. So, with increasing age, the difference in the indicators of the DMFT index increased.

In all age groups, a statistically significant difference was determined between the data on the intensity of dental caries in the control and the main observation groups.

When assessing the DFT index in the age group of 3-5 years old the DFT index was 9.41 ± 0.62 in main group and 6,82±0,75 in control group. The average value of the index in the main group was 1.4 times higher than the average value in the control group ($p < 0.05$). When analyzing the DFMT + DFT index in the age group of 6-12 years old, the DMFT index was 9.75 ± 0.35 in the main group. The average value of the index increased twice in patients with BTM ($p < 0.001$).

Analysis of the index of the intensity of permanent teeth caries in the second group with a mixed dentition showed that each patient with thalassemia has their permanent teeth affected by caries.

At the same time, the average indicator of the DMFT index in the main group was 2.20 ± 0.15 versus the average value of 1.6 ± 0.08 in the control group ($p < 0.001$). The total value of DMFT + DFT was equal to 9.75 ± 0.35 in the main and 4.84 ± 0.25 in the control group.

In the third age group, the mean value of the DMFT index in patients with thalassemia was 6.84±0.25 and 3.91±0.30 in healthy group. The mean value of main group was also significantly differed and was 1.8 higher than in the healthy group ($p < 0.001$).

When interpreting the indicators of the index in the fourth age group (≥18 years), it was found that, the average value of the DMFT index in the main group was is 9.18±0.26 and it was 1.5 times higher than the average value in the control group (6.31±0.3, $p < 0.001$).

The data obtained indicate a more pronounced degree of carious lesions of the teeth in all main groups.The results of evaluating the components of the index DMFT, DMFT+DFT, DFT, are presented in Table 1.

Table 1

The structure of the DMFT index in the surveyed groups

Age groups	Average number of teeth M ± m					
	Carious		Filled		Missed	
	Main	Control	Main	Control	Main	Control
3- 5 years old	9,41±0,62 ***	6,24±0,70		0,45±0,70		-
6-12 years old	9,09±0,40 ***	4,15±0,26	0,24±0,05 ***	0,73±0,09	0,09±0,03	0,08±0,02
3-17 years old	5,93±0,24 ***	2,54±0,21	0,70±0,11 ***	1,18±0,14	0,21±0,06	0,21±0,06
≥18 years old	6,28±0,23 ***	3,41±0,27	2,02±0,19	2,55±0,25	0,89±0,11 ***	0,36±0,07

Note: the statistical significance of the difference in the indicators of the control group was determined by the Kruskal-Wallis test: * -p <0.05; ** - p <0.01; *** - p <0.001.

When studying the primary teeth caries activity in the first age group of patients with BTM, the degree of caries incidence was 9.41 ± 0.62. This group also had the highest percentage of untreated carious teeth, which indicates a low level of visits to a dentist at this age. In the control group of the same age, the index of filled teeth was 0.45 ± 0.70.

In the structure of the DMFT index in a mixed dentition stage (6-12 years), component D in patients with BTM 9.09 ± 0.40 and was 2 times higher than this indicator in the control group (4.15 ± 0.26, p <0.001). The proportion of filled teeth was 0.24 ± 0.05 in the BTM group and 0,73±0,09 in the control group. In children of the main group with permanent occlusion, the number of teeth affected by caries averaged 5.93 ± 0.24 versus the average value of carious teeth in the healthy group 2.54 ± 0.2 (p <0.001). The proportion of treated teeth in the BTM group was 0,70±0,11, and in the control group - 1,18±0,14.As for the premature extraction of permanent teeth in these groups, their indicators are very low and do not have a statistically significant difference. On average, this indicator was 0.21 ± 0.06 in both the main and control groups.

The study of the structure of DMFT in the adult group ≥18 years old showed that in patients with BTM, carious teeth significantly prevailed - 6.28 ± 0.23 versus 3.41 ± 0.27 in the control group. The average number of filled teeth was 2.02 ± 0.19 in the main group and 2.55 ± 0.25 in the control group.

The number of extracted teeth was significantly higher in the group of patients with thalassemia, making 0.89 ± 0.11 versus 0.36 ± 0.07 in the control group. Thus, in the age aspect, there is a significant increase in the extracted teeth in comparison with similar data in the somatically healthy group.

The analysis of the DMFT index components showed the prevalence of the percentage of carious teeth over the filled ones in the first and second age groups of healthy patients and a significant predominance of untreated teeth in all four groups among patients with BTM. 30 young and adult children from 256, had permanent teeth extracted (corresponding to 10%). We found that in children with BTM, the prevalence and intensity of dental caries decay is 2 times higher than in practically healthy children

Thus, children with BTM have high rates of dental caries prevalence and intensity with a significant predominance of untreated teeth, which indicates shortcomings in the organization of dental care for such patients.

The study of oral cavity biocenosis with an assessment of oral fluid microflora activity showed a significant increase in the quantitative indicators of anaerobic bacteria (Porphyromonas gingivalis), yeast-like fungi (Candida) and microbial associations in patients with thalassemia. In practically healthy individuals of the control group, different from hematological patients, the structure of the microbiocenosis of the mixed oral fluid was stable and was mainly represented by Lactobacillus spp., Streptococcus spp., Staphylococcus spp. and Enterobacteriaceae. Indicators of anaerobic microflora also exceeded the permissible limits of the norm. The microbiological study, which revealed a significant increase in the quantitative and qualitative indicators of periodontopathogens in the main group, showed a decrease in the local anti-infectious resistance in the oral cavity in thalassemia, as a sign of local and systemic

immunological disorders and dysbiosis. The established facts play the essential etiological role in the development of inflammatory diseases of periodontal tissues in patients with BTM.

Results of the study of the orthodontic status pecularitis in patients with β-thalassemia major.

In BTM, dysfunction (hyperfunction or hypofunction) of all endocrine glands leads to disruption of mineral metabolism in bone structures. This fact is unlikely not to be reflected in various violations of the shape and size of the jaws and in severe maxillofacial deformities. When determining the bone age (analysis of the appearance of the nuclei of ossification of the distal epiphyses of the bones on the roentgenogram of the bones of the hand), a discrepancy between the passport age and the degree of formation and calcificaton of bones is revealed in all cases.

In most cases, patients with BTM had a characteristic "Mongoloid" appearance due to an increase in the distance between the orbits and a narrow cut of the eyes, deformation of the skull due to the thickening and standing of the parietal and occipital bones, expansion of maxillary body and zygomatic bones, an alteration in the configuration of the midface zone due to the flattening of the nasal bridge. Almost all patients were found to have anomalies in the position of certain teeth and a violation of the ratio of the jaws in all three planes.

When assessing the orthodontic status, the prevalence of dento-alveolar anomalies in patients of the main group was revealed. In assessing the jaw ratio, the results of examination of patients with BTM are as follows: in the sagittal direction, Angle class I was found in 88 patients (27.4%), class II with incisor protrusion - in 210 patients (65.4%), class II with incisor retrusion - in 22 (6.9%) patients, class III - in 1 patient (0.3%); in the vertical direction, vertical incisal disocclusion was more common - in 242 patients (75.4%), deep incisal occlusion - in 62 patients (19.3%), direct overlap in 17 patients (5.3%), in the transversal direction, cross-bite occurred in 8 patients (2.5%).

The following types of anomalies in the position of certain teeth of BTM patients were identified - crowding in 63 patients (19.6%), dystopia in 51 patients (15.9%), adentia in 10 patients (3.1%), retention in 9 patients (2.8%), supernumerary teeth in 2 patients (0.6%). In 283 patients, discoloria (tooth discoloration) was revealed (88.2%) and in 38 patients (11.8%) a wedge-shaped defect was revealed.

When analyzing the timing of the eruption of permanent teeth in children with β-thalassemia, a delay in their eruption was noted on average from 6 to 24 months. Also, there was a violation in the sequence of eruption of permanent teeth for 3.2% of all the examined patients.

The most common anomaly of the occlusion in dentition was the violation in molars closure according to the Angle class II, though statistically significant differences in violations in males and females were not noted.

While studying the prevalence of closure disorders of the first permanent molars in terms of age, the following data were found:

- in the first age group (3-5 years) in 46 children of the main group (78%), and in the control group in 27 children (81.8%), a closure of the molars of the Angle class I was identified. In 12 children (20.3%) of the main group and 5 (15.2%) of the control group, the mandibular distal position was noted. In the control group, one case (3%) of mesial occlusion was registered.
- in the second age group (6-12) 36 children (25.7%) of the main group and 80 children (44.7%) of the control group had a neutral bit occlusion (Angle class I). The ratio of class II first molars with incisor protrusion was observed in 101 patients (72.1%) of the main group and 72 patients (40.2%) of the control group. The ratio of class II jaws with incisor retrusion was observed in 3 children (2.1%) in the main group and in 18 children (10.1%) in the control group. Class III ratio was observed in 9 (5.0%) healthy patients and did not occur among thalassemic patients.
- in the third age group (13-17 years) 2 patients (3.5%) in the main, and 35 patients (41.2%) in the control groups had a neutral bit occlusion e (Angle class I). The ratio of the first molars class II with

incisor protrusion was observed in 45 patients (78.9%) of the main group and 41 patients (48.2%) of the control group. The ratio of class II jaws with incisor retrusion was observed in 9 (15.8%) patients in the main group and in 6 patients (7.1%) in the control group. Class III ratio was observed in one (1.8%) patient of the main and in 3 (3.5%) patients of control groups.

- in the fourth age group, the ratio of class I molars was in 4 adult patients with BTM (6.2%) and in 36 patients (42.4%) in the healthy group. The ratio of the Angle class II jaws with incisor protrusion significantly prevailed with occurrence of 52 (80%) in thalassemic patient group. In the control group, this ratio was found in 34 persons (40.0%). The ratio of Angle class II jaws with incisor retrusion was observed in 9 thalassemic patients (13.8%) and in 9 healthy persons (10.6%). The ratio of the Angle class III first molars was observed only in 6 (7.1%) adult patients of the control group.

Analysis of these anomalies in the shape and size of the dental arches of patients allows to come to conclusion that they are associated with an increase in the size and expansion of the upper jaw, which leads to protrusion of the teeth, inclination of the incisors and the formation of a sagittal gap and resulting in crowding and tight position of certain teeth in some cases.

In cephalometric analysis of angular and linear parameters characteristic to growing patients with BTM, we revealed the presence of skeletal pathology according to Angle class II: (∠SNA = 78.1 ° ± 0.9, ∠SNB = 71.5 ° ± 0.6 ∠ANB = 6.6 ° ± 0.6). Dental maxillary anomalies in patients with BTM are characterized by micrognathia - a decrease in the maxillary body (GoGn = 62.9 ° ± 0.8 mm).

The value of inclination angle of the skull base (NSBa) in patients with BTM differs from the value of this angle in patients of the control group, due to a slight decrease in the size of the skull in this patient contingent. Increased vertical angular parameters in the group of BTM patients (total angle Bjork, ∠NSL-ML, ∠ML-NL, ∠NGoMe) characterize the vertical type of growth of the facial skeleton. In adult patients, the skull base angle (NSBa) is enlarged, and there is a tendency towards skeletal class II due to protrusion of

the naso-maxillary complex and rotation of the mandible to the posterior position (rotation back). A statistically significant increase in the angular parameter ANB, obtained in BTM patients indicated an abnormal deviation of the position of the jaws relative to the base of the skull which corresponded to Angle class II for sagittal anomalies. The patients also had a delay in the development of the anterior base of the skull (S - N; P <0.01). Significant differences in comparing the results of measuring the SArGo angle indicate the distal position of the articular head of the mandible in BTM patients. Also, in this group, the position of the upper jaw in the sagittal plane remained within the normal range (∠SNA = 79.0 ° ± 0.9), while a decrease in the angles (SNB, SNPg,), due to the retro position of the lower jaw relative to the skull base, was noted. When comparing the transverse dimensions of the jaws, a decrease in the size of the maxillary body and ramus was revealed. A decrease in the distance of the anterior segment of the base of the skull (SN) and the posterior length of the skull base (SAr) in the main group compared with the control group. As for the dento-alveolar relations, in the group of thalassemic patients, a slight decrease in the inter-incisal angle and the inclination of the lower incisors to the lower jaw were revealed. There was no statistical difference in other parameters (overjet, overbite). Analysis of the soft tissue data revealed a convex facial profile in BTM patients. Thus, both linear measurements of the position of the upper and lower lips in relation to the aesthetic plane were increased (UL-El, LL-El). However, the nasolabial angle (ClSnUl), which is an important criterion in facial aesthetics, was less in the main group (p <0.001).

The results of cephalometric analysis showed that patients with BTM in younger and older age groups differ from healthy subjects of the same age, gender and ethnicity. There is a slight increase in the maxillary bone in the sagittal direction, which does not affect the position of the upper jaw. The dimensions of the head and upper jaw also decrease, generally, in comparison with the standard values. Basically, we observed shortening of mandibular ramus, underdevelopment of the alveolar processes, hypertrophy of bone tissue in the lateral areas of the upper jaw. We noticed the

pronounced disharmony of the facial skeleton, depending on the age of the patients. So, in children, there was a noticeable overdeveloped maxillary bone in the molars and the gaps between the frontal teeth. And in older patients, a developed mandibular body and shortened ramus of the lower jaw were observed. The excessive discrepancy between the size of the upper and lower jaw decreased with age.

Therefore, adequate transfusion therapy in time prevents severe clinical manifestations of BTM. The cephalometric data observed in patients with BTM in Azerbaijan indicate a tendency only to a reduced size of the mandible and vertical growth of the mandible. Overall, this indicates a decrease in complications over the past decades, associated with early diagnostics, treatment and regular follow-up.Thus, detection in time of the characteristic pathological disturbances in the maxillofacial region of patients with BTM can contribute to early diagnostics and complex treatment.

For the further development of morphometric differential diagnostics of patients with BTM, we studied the upper respiratory way indicators obtained on the lateral cephalograms of the skull.

Taking into account such craniofacial parameters as the position of the upper and lower jaw to the base of the skull, the inter -maxillary relationship, the type of jaw growth, the control group included patients with a neutral occlusion according to Angle class I with an inter -maxillary angle ANB of 0-2º.

When comparing TRG of patients with BTM and patients with a neutral occlusion, the following was revealed:

- the angular parameters of the jaws revealed the most posterior position of the lower jaw in relation to the skull base in the main group, resulting in a significant increase in the inter -maxillary angle ANB ($P < 0.001$).

- in the main group, there was a decrease in the following vertical dimensions of the facial region of the skull compared with the control group: the upper anterior face height N-ANS ($P < 0.05$) and the posterior face height Go-CF ($P < 0.05$).

- the average values of the radiographic length of the tongue were 65.9 ± 1.8 mm in patients with BTM and 70.8 ± 2.6 mm in

subjects of the control group. The difference was statistically significant (P <0.05).

- the length index of the soft palate (PNS –V) was significantly less in patients with BTM (56.1 ± 2.1 mm. P <0.05) than in those with a neutral occlusion (61.4 ± 1.8 mm).

- the vertical size of the airways was 28.6 ± 0.9 mm in the BTM group, which was significantly less than this indicator in the control group (31.8 ± 3.9 mm P <0.001).

- comparing the size of the pharynx revealed a significant decrease in the upper (P <0.05), middle (P <0.05) and lower width (P <0.01) of the upper airways in BTM patients compared with patients with neutral occlusion.

- the distance from the hyoid bone to the mandibular plane (H-MP) and the vertical distance between the hyoid bone and the symphysis of the mandible (H-RGN) were also shorter in BTM than in the control group (P <0.001).

The study confirmed the hypothesis on the pathological effect of the position of the mandible on the diameter of the upper airways. Thus, in the examined contingent, a positive correlation was observed between the SNB angle, which reflects the ratio of the mandible to the anterior base of the skull, and the width of the airways. The distal position of the mandible correlated with the narrowing of the upper airways. In BTM patients, the length of the vertical airway was also shorter, and the hyoid bone was closer to the plane of the mandible.

The present study revealed a decrease in the lumen of all parts of the upper airways and tendency to narrowing of the lower respiratory space (IAS) in BTM patients. Thus, the hypothesis on the pathological influence of the position of the mandible on the diameter of the upper airways was confirmed. These results can be explained by the fact that BTM patients have noticeable growth retardation caused by various environmental factors, including severe chronic anemia, endocrine dysfunction, and somatomedin deficiency, which is noted in the period nearer to puberty. The adenoid type of face, especially marked in patients with BTM, occurs due to ineffective erythropoiesis and erythroid hyperplasia of the bone

marrow and cranio-facial structure changes. The established facts are of great importance in predicting the development and course of the pathology of the ENT organs and the entire respiratory tract in thalassemic patients, affecting the quality of their life. The study revealed the necessity of the organization of interdisciplinary interaction between dentists, ENT specialists and internists in the complex supervision and dispensary observation of patients with β-thalassemia.

Anthropometric analysis of craniofacial soft tissues peculiarities in patients with BTM were also done during the study. The values of the craniofacial ratio indices were compared with the control group, which included the data on the norms of a healthy group of persons identical in gender, age and ethnicity. At the same time, a database of Caucasians was taken as a basis, using the anthropometric parameters of Azerbaijanis.

The obtained mean values of the craniofacial complex soft tissue anthropometric linear parameters in patients with BTM presented deviations from the data of the control group in 26 parameters in women and in 28 parameters in men.

A quantitative analysis of the craniofacial soft tissues allowed to conclude that patients with BTM are characterized by: head enlargement in transverse dimensions, mandibular narrowing, shortening of the mandibular branch growth; flattening of the nose bridge, narrowing of the nasal root, orbital hypotelorism, orbital protrusion, protrusion of the vertical contour of the upper lip.

The saddle shaped nose can also be explained by the underdevelopment of the cranial base in the anteroposterior direction and maxillary underdevelopment in the region of the nasal process resulting in depressed mid face. Despite the general retardation in the growth of the cranium, in comparison with the rest of the patient's body parts, the head proportionally looks bigger. In the course of anthropometric studies in adult patients, we observed more pronounced and diverse changes in the facial soft tissues in comparison with changes in bone parameters. This fact can be explained by edema of the facial soft tissues and mucous membranes, which was confirmed by electron microscopic studies. Swelling of

the soft tissues also gives a smoother and stiff appearance to patients with thalassemia.Thus, timely detection of characteristic pathological disorders in the maxillofacial region in patients with BTM can contribute to early diagnosis and rational planning of orthodontic and surgical treatment of craniofacial deformities. The study of morphological disorders of the craniofacial complex in patients with thalassemia is important for further determining the duration and regimen of blood transfusions in the treatment of this contingent of patients.

Results of the study of homeostatic disorders in patients with BTM

In the homozygous form of BTM, the study of homeostatic disturbances, which play an essential role in the development of dental pathology, is of great diagnostic value. To solve this problem, we conducted a laboratory analysis of the blood serum of 58 persons with BTM and 16 practically healthy respondents of the control group.The research findings of iron metabolism in the blood of the examined groups showed an increase in the content of SI and ferritin against the progressively decreasing TIBC of blood in patients with BTM.

Thus, the level of SI in all age groups of patients with BTM was twice as high as in the control group ($p < 0.001$). Serum transferrin levels were extremely high. In the youngest age group of patients with BTM, the amount of transferrin was 734.9 + 69.2 ng / ml 19.3 times higher than in the control group. In the second age group, it was 967.5 +42.8 ng / ml, 16.6 times higher than in the control group. The amount of transferrin in the main group of 13-17 years old was 1077.7 + 62.6 ng / ml - 13.7 times higher than the transferrin indicators of the control group, and in the 4 main group the indicators were 1062.7 + 100.7 ng / ml, thus,19.4 times higher than the indicators of the control group ($p < 0.001$).,

The values of TIBC, LIBC were increased, and the values of UIBC were elevated in all age groups ($p < 0.001$).

Also, in BTM patients, a simultaneous increase in the blood level of hepcidin, a multifunctional regulator of iron metabolism,

participating in the suppression of the microbial factor and in the activation of cytokine cascades of inflammation, was noted.

Thus, the average level of the hepcidin index among the surveyed in the first age group was 18.5 + 1.3 ng / ml, which was 1.6 times ($p < 0.05$) higher than in the control group. In the second age group, the hepcidin index of 26.4 + 1.4 ng / ml was 2.4 times higher ($p < 0.001$) than that of the control group. In the third age group, the hepcidin index was 32.3 + 2.0 ng / ml and turned out to be 2.4 ($p < 0.001$) times higher than the indicators in healthy respondents and, accordingly, in the fourth group, 40.1 + 2.1 ng / ml. ml, 3.5 times higher ($p < 0.001$). Thus, among the entire surveyed contingent, 56 patients (96.6 ± 2.4%) had indicators above the norm.

The study revealed that despite the chelation therapy using desferal resulted in the reduction of the risk of hemosiderosis, this problem could not be completely solved. With an increasing age, excessive free iron accumulation in homozygous patients is accompanied by an increase in the level of hepcidin in the blood. (chart 2).

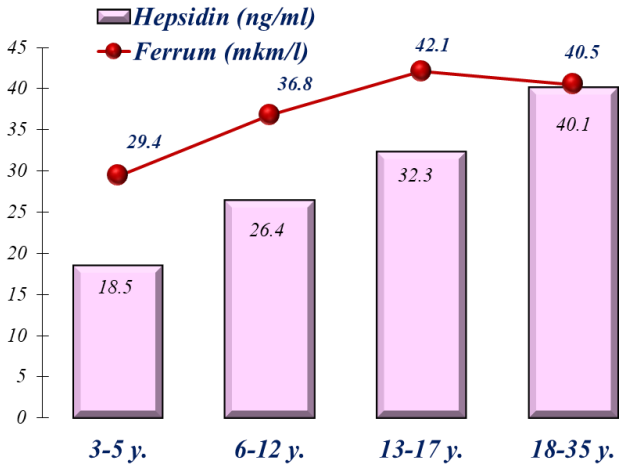

Chart 2. Dynamics of iron metabolism indicators depending on BTM patients age

As a result of our study, statistically significant differences were revealed between the indicators of hormones and mediators that regulate phosphorus-calcium metabolism in the main and control groups.

Thus, it was found out that in all age groups of patients with BTM, the levels of calcium and parathyroid hormone in the blood were significantly reduced ($p < 0.01$). At the same time, the indicators of phosphorus, osteopontin, osteocalcin, calcitonin, alkaline phosphatase were several times higher than in healthy respondents.

A dynamic decrease in the blood calcium level against a significantly high ($p < 0.001$) content of phosphorus corresponds to a low level of parathyroid hormone in the blood ($p < 0.001$), which allows to associate the revealed mineral metabolism disturbances with functional insufficiency of the parathyroid glands.

The correlation analysis enabled us to establish a high level of direct dependence (r-from +0.5 to +0.7) of iron, calcium, phosphorus metabolism disturbances with a decreased level of parathyroid hormone in the blood increasing with age, which proves the interrelation between calcium and phosphorus exchange disturbances and hemosiderosis of the parathyroid glands.

A specific feature was the simultaneous increase in the level of calcitonin in the blood - a functional antagonist of parathyroid hormone. Osteosclerosis, manifesting overproduction of calcitonin, associated with osteoporosis, is characteristic for bone abnormalities in BTM. The increase of osteontin and osteocalcin content in blood of all patients with BTM indicates that the content of osteoforming factors in blood increasing with age, is obviously of a compensatory nature.

The predominantly inflammatory nature of the diseases, replenishing the composition of polymorbid pathology in BTM patients in the duration of life, required an assessment of the cytokine profile in the observed patients. Thalassemic patients were characterized by a dynamic increase of both pro-inflammatory and anti-inflammatory cytokines. (Table 2)

Table 2

Age indicators of the pro and anti –inflammatory cytokine level and ratio dynamics in BTM patients

Indicators	Observation group				Control group
	3-5 years	6-12 years	13-17 years	<18 years	
IL-2	1,2±0,27 ***	1,71±0,17 ***	2,28±0,27 ***	2,21±0,21 ***	0,34±0,08
IL-6	6,8±2,0 *	10,3±0,9 ***	9,5±1,2 ***	9,1±1,1 ***	2,3±0,8
IL-10	12,49±4,58	13,44±1,49 **	19,56±3,32 ***	14,28±1,82 **	6,09±1,46
TNF–α	1,44±0,36 *	1,79±0,15 ***	2,36±0,22 ***	2,49±0,23 ***	0,59±0,14

Note: the statistically significant differences in the indicators with the control group was determined by the Kruskel-Wallis test: *-$p<0.05$; **-$p<0.01$; ***-$p<0.001$.

Obviously, the predominance of the anti-inflammatory component in the activated cytokine cascades contributes to the demarcation of local inflammatory processes, including the oral cavity, and is probably the most important factor in the "survival" of homozygous patients with β-thalassemia generally in conditions of multifactorial metabolic disorders.

In addition to the function of regulating iron homeostasis in the body, hepcidin is a mediator of innate immunity, playing the role of an important antimicrobial factor and suppressing microbial inflammation by reducing the supply of iron to the lesion[25].

The evidence of the functional inclusion of hepcidin in the cytokine cascades of inflammation in patients with thalassemia is the established pronounced correlations with IL-2, TNF-α, IL-6 in different groups (Table3).

[25] Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics, –2014. № 6 (4)– p.748–773.

Table 3

Correlative relationships between cytokine profile indices and iron metabolism parameters

Indicators	SI	TIBC	LIBC	Ferritin	Hepsidine
IL-2	,307 *	,072	-,139	,333 *	,553 **
IL-6	,316 *	,409 **	,021	,394 **	,432 **
TNFα	,573 **	,261 *	-,300	,592 **	,719 **

Note: ** Correlation is significant at the 0.01 level
* Correlation is significant at the 0.05 level

The study established significant correlative dependence between cytokines determining the course of the inflammatory process and calcium metabolism indicators seriously impaired due to hemosiderosis of the parathyroid gland in thalassemic patients' organism.

Negative correlation of low parathyroid hormone levels with high levels of inflammatory cytokines was presented. Thus, an inverse correlation was observed between the level of parathyroid hormone and the level of cytokines IL-2, IL-6, TNF-α (respectively $\rho = - 0.372$ $p < 0.01$; $- 0.260$ $p < 0.05$; $\rho = - 0.572$ $p < 0, 0$

The negative correlation of parathyroid hormone level with hepcidin parameters was also natural (ρ ranged from -0.36 to -0.53 in different age groups).

The study of the metabolic characteristics of patients with thalassemia led to the conviction that complex combined disorders of mineral metabolism (iron, calcium, phosphorus) are associated with the initiation of systemic mechanisms of inflammation. The balance of cytokines in cytokine cascades directs the inflammatory process and determines its outcome. The established metabolic disorders that contribute to systemic inflammation in the body can be considered as potential targets for targeted pathogenic multimodal therapy in polymorbid patients.

Mineral metabolism disorders are associated with the activation of cytokine cascades of inflammation and are highly correlated with them.

The results of light-optical and electron microscopic study of the lamina propria in the mucous membrane of free part of the gums in patients with BTM.

Gingival biopsies taken from 18 patients with BTM revealed the signs of various forms of chronic gingivitis (catarrhal-sclerosing, sclerosing and ulcerative-necrotic). The predominant form (14 out of 18) has been determined to be catarrhal-sclerosing chronic gingivitis (CSCG) (5- in remission and 9- in exacerbation) because of both the study at the light-optical and electron-microscopic levels.

The obtained factual material presents a close relationship between the severity of the inflammatory process and the keratinization degree of the epithelial cover, as well as the ferritin overload of macrophages of the gingival lamina propria in patients with BTM.

It is noted that the ferritin molecules themselves, and particularly its protein part, apoferritin can be detected on unstained ultrathin sections only with the help of an electron microscope magnification of 100,000-fold or more. Both ferritin molecules, separately and structures related to siderosomes and hemosiderin, are found in the cytoplasm of all cellular elements involved in the formation of the gum, its nutrition and innervation.

The iron-containing ferritin core is revealed as a black point in ultrastructure and the apoferritin coating as a light (osmio-phobic) ring (Fig. 1A).

The level of gray intensity (gray value) at site of apoferritin in the ferritin molecule fluctuates between 6250 and 6600, and at the top of the iron mineral, this indicator drops from 4800 to 5400 (Fig.1B). On the one hand, this makes it much easier to clarify whether osmiophilic formations, according to their size, belong to the ferritin molecule and on the other hand, it allows to more accurately determine the degree of iron accumulation in the organism of BTM patients.

Except the cytosol of cellular structures involved in the formation of the free part of the gums, ferritin molecules are also found in their mitochondria, lysosomes, nucleoplasm, as well as on the nuclear membrane. The presence of siderophages with hemosiderin accumulations in various transparency degree in BTM indicates the presence of natural and denatured forms of ferritin in the cells of both the lamina propria (Fig.1B) and the epithelial cover of the free part of the gum (Fig.1 G) as well as the other organs.

Thus, the determination of the molecular mechanisms of ultrastructural rearrangements in the formation of extra and intracellular transportation storage methods, as well as the pathways that ensure the bioavailability of ferritin, can significantly increase the diagnostics, prevention and treatment of hemochromatous conditions, including BTM.

The established features of ultrastructural changes in the periodontium in patients with BTM are morphological substrates of the dystrophic component formed during degenerative-dystrophic processes in the periodontal tissues.

It should be emphasized that all types of mononuclear cells expose various degrees of phagocytic activity, particularly macrophages (Fig. 1B and 1G) and Langerhans cells (Fig. 1D), in the cytoplasm of which heterophagosomes and phagolysosomes are found.

From polymorphonuclear cells, neutrophils are the main cellular elements of innate immunity, playing an irreplaceable role in ensuring hemostasis of the oral cavity organs[26], and migrating into the epithelial cover of the gums, they perform a barrier function against dysbiotic bacteria in the oral cavity[27].

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[26] Cortés–Vieyra, R. Neutrophil Functions in Periodontal Homeostasis / R.Cortés–Vieyra, C.Rosales, E.Uribe–Querol / Journal of Immunology Research, – 2016, Article ID 1396106, 9 p

[27] Nussbaum G., Shapira L. How has neutrophil research improved our understanding of periodontal pathogenesis? // J Clin Periodontol, – 2011. № 38 (11)– p. 49–59.

It should be emphasized that in the stage of exacerbation of chronic catarrhal sclerotic gingivitis (CCSG) any ultrastructural indicators characterizing their functional activity (the presence of numerous micro outgrowths, degranulation, the formation of an extracellular neutrophil trap, designated NETs (Neutrophil Extracellular Trap), signs of phagocytosis and apoptosis) were not observed during the study (Fig. 1E)

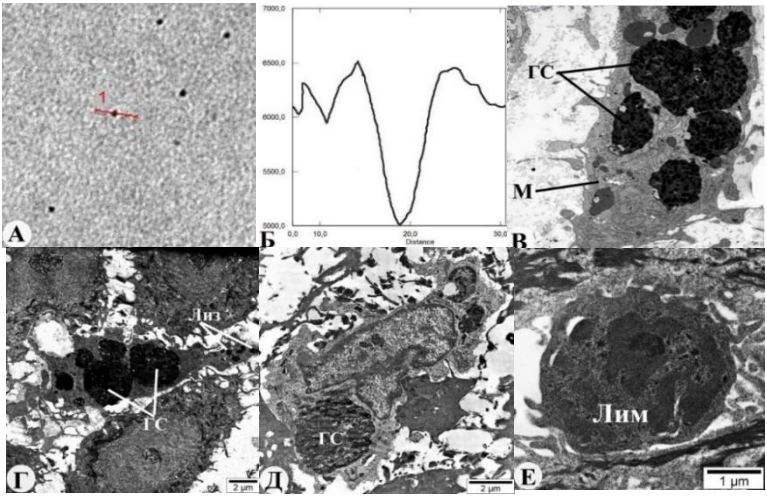

Fig. 1. Ultrastructure (A) and histogram (B) of certain ferritin molecules and the accumulation of denatured forms of ferritin in the cellular elements of the gums in patients with BTM (B-E). A and B-E electronograms of ultrathin slices (staining with 2% uranyl acetate and 0.6% pure lead citrate).

Multiple accumulations of ferritin are found in the cytosol of mast cells; they are found both in separate molecules and also in the epithelial cells of the gingiva. At the same time, despite careful examination of unstained ultrathin sections, we did not observe the presence of neutrophils in their composition.

It should be emphasized that along with the molecules of ferritin, siderosomes and hemosiderin, we revealed ferritin cores that have lost their apoferritin coating, both in the cytoplasm and in the

nucleoplasm of immunocompetent cells, among which macrophages, monocytes and lymphocytes are predominant (Fig.2A). It should be noted that the presence of destructive changes in monocytes, which according to modern data is the source of the formation of immunocompetent antigen-presenting cells - macrophages, dendritic cells (Langerhans cells) and even fibrocytes[28], the number of which sharply increases in the exudative phase of exacerbation of chronic sclerotic gingivitis.

In the stage of exacerbation of CCSG, changes occur in the thickness of the epithelial gingival covering, leading to the appearance of slit-like intercellular spaces (Fig.2B), which are described as a manifestation signs of acantholysis of the gingival epithelial covering[29].

Analyzing the data obtained, it should be emphasized that despite the lack of a consensus on the molecular mechanisms, the integrity of the epithelial cells themselves is not violated during acantholysis.

According to Grando S., acantholysis appears due to the destruction of molecular bonds of the intercellular desmosomal consolidations caused by phosphorylation of adhesion molecules, resulting in separating cellular membrane parts involved in the formation of desmosomes[30].

Summarizing the above data, we can conclude that in the exudative phase of CCSG in patients with BTM, the formation of expanded slit-like spaces of various shapes and sizes in the gingival epithelial cover should be considered as a sign of spongiosis, which

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[28] Reilkoff, R.A., Bucala R., Herzog E.L. Fibrocytes: emerging effector cells in chronic inflammation. //Nature reviews Immunology, –2011.№11(6) –p. 427–435.

[29]Лушникова, Е.Л., Бакулин И.И. Ультраструктурный анализ слизистой оболочки десны при хроническом воспалении. // Бюллетень Сибирского отделения РАМН, – 2008. № 6. – с. 125 – 131.

[30] Grando, S.A., Bystryn J.C., Chernyavsky A.I. et al. Apoptolysis: a novel mechanism of skin blistering in pemphigus vulgaris linking the apoptotic pathways to basal cell shrinkage and suprabasal acantholysis. // Exp Dermatol,– 2009 №18(9) –p. 764–770.

has arisen due to the spread of edematous fluid (transudate) from the papillary layer of the lamina propria, where an increased permeability of thin walled micro vessels (especially postcapillary venules) is total [21].

Smoothing of the basal surfaces of keratinocytes and a significant increase in the volume of intercellular spaces (spongiosis) due to edematous fluid leads to a decrease in the metabolic processes between the lamina propria and the epithelial covering of the gum, and to pronounced hypoxia of the latter in the exudative phase of CCSG.

Due to the disruption of tonofilamento-desmosomal complexes in the semi-desmosomes (in Fig.2B marked PD) of the basal surface and desmosomes of the remaining surfaces of the basal layer of gingival epithelial cells called collapse also including the retraction of tonofilaments[31], a decrease in the total volume of the epithelial cells cytoplasm (Fig.2G) , deformations of various degree in nuclei and the absence of both delicate and thickened bundles of tonofilaments in direct vicinity of the epithelial cells membrane (in Fig. 2B marked by arrows) have been revealed.

As can be seen from Fig. 2D in the prickly and granular layers of the epithelial covering, more than half of the cytoplasm is occupied by accumulations of glycogen granules (in the Fig. marked GL).

It should be emphasized that in the granular layer, thickened bundles of tonofilaments (in Fig. 2E marked by arrows) are in contact with accumulations of glycogen in the site of keratohyalin granules (in Fig. 2E marked with snowflakes).

Foci of sequestration and lysis of glycogen accumulations lead to the vacuolization of the perinuclear and peripheral parts of the cytoplasm of the prickly and granular layers epithelial cells (in Fig. 2B marked Bak), which are also visible at the light-optical level (Fig. 2D).

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[31] Seshadri, D., Kumaran M.S., Kanwar A.J. A cantholysis revisited: back to basics. // Indian J Dermatol Venereol Leprol, –2013. №79(1) –p. 120–6.

If the stratum corneum is formed at least by 4 layers of corneocytes at the stage of CCSG remission, then at the stage of exacerbation in the stratum corneum, along with the formed corneocytes (in Fig.2 marked by single arrows) the cells without any signs of keratinization – light cells (in Fig. 2E marked paired arrows) may also be found out.

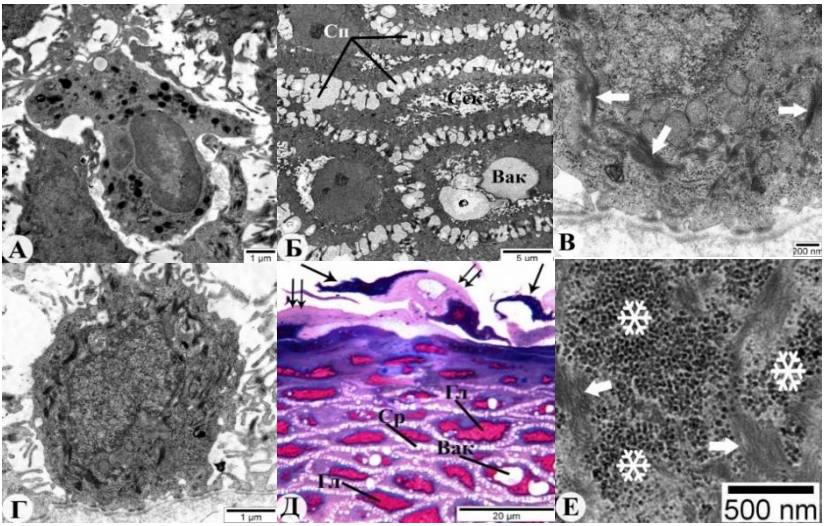

Fig. 2. Ultrastructural (A-G and E) and microscopic (D) structural features of the cellular elements of the gums in patients with BTM. A-G and E electronograms of ultrathin slices (staining with 2% uranyl acetate and 0.6% pure lead citrate), D – micro photo of a semi-thin slice (trichromic staining).

With the destruction of cytoskeleton elements and the accumulation of glycogen granules in the cytoplasm of keratinocytes, as a biological barrier is disrupted, the stratum corneu of the epithelial coating is formed, resulting in the formation of long - lasting wounds in the gingival mucosa of patients with thalassemia.

The ultrastructural study allowed us to establish signs of serious functional disorders of connective tissue cells, primarily fibroblasts that synthesize collagen. It should be taken into

consideration that the inflammatory - degenerative process in periodontal tissues in BTM patients lasts in most severe oxidative stress condition induced by chronic anemia and hemosiderosis.

Oxidation of proteins by free radicals leads to accelerated degradation of the protein structure of collagen, destroys the "cross-links" of collagen fibers, which entails structural disorganization of the connective tissue with the destruction of its framework[32].

As a result, a pronounced disorganization of the connective tissue is formed with destructed collagen framework and insufficient immunocompetent cells in its matrix, which serves as a histological basis for dystrophic component of the inflammatory process in BTM patients' inflammatory periodontal diseases.

Analyzing the data obtained, at first sight, it can be concluded that transformations identified in the gingival structural elements in the exudative phase of exacerbation of catarrhal-sclerosing chronic gingivitis, as a primary acute inflammatory process accompanied by a sharp increase in vascular permeability may be considered as a response to pathogenic factors due to the release of vasoactive substances secreted by mast cells and macrophages .

However, accumulation of a sufficient amount of hemosiderin in the cytoplasm of macrophages, regardless of their location, the identified heterophagosomes occupying more than half of the cytoplasm of Langerhans cells and a sharp keratinization disruption (almost the absence of differentiated corneocytotes) indicate the presence of a chronic process, but only in the stage of exacerbation. The factual material presented in the study indicates that not only in the exudative stage of exacerbation of chronic gingivitis in patients with BTM the presence of plasma cells, being one of the main effector populations of acquired immunity cells, is rarely found out. These facts can be assessed as the disturbance in the mechanisms of acquired immunity in BTM patients.

[32] Pirte, A., Vaida L., Venter A. et al. Ultrastructural modifications at the level of marginal periodontium in the case of incorrect dental reconstruction // Rom J Morphol Embryol, – 2009. № 50(4) – p. 683–687.

In fact, in the exudative phase of exacerbation of catarrhal-sclerosing chronic gingivitis in the structural elements of the gums, the main cellular elements are neutrophils, macrophages and activated fibroblasts. According to modern data, the interaction of these cells may principally impact the development of acute inflammation, having a nonspecific and stereotyped character and thereby carry out the processes characteristic of innate(non-adaptive) immunity.

Thus, the study of biopsy material using modern methods, as well as the identification of molecular mechanisms underlying the interactions the cellular elements involved in the innate immunity responses can be used to develop the new methods in diagnostics and treatment of inflammatory processes in patients with BTM.

Basing on the obtained data, it becomes obvious that in order to increase IPD (Inflammatory Periodontal Disease) prevention and treatment efficiency in BTM, it is necessary to therapeutically organize conditions for the correction and optimization of connective tissue cells functions to ensure the synthesis of complete collagen, as well as to stimulate the anti-infectious resistance of the periodontium. This is available by replenishing the essential macro and microelement deficiencies, as well as supplementing therapeutic measures with appointment of antioxidants and agents that mobilize local anti-infectious protection.

The effectiveness of integrated approaches to dental treatment of patients with BTM.

The interrelation between metabolic disorders and cytokine imbalances established in the study motivates to research the new means of multimodal therapy that can cut the vicious circle of mutual potentiation of systemic inflammatory factors to prevent the progressive poly -morbidity.

Due to comprehensive examination of patients with BTM during the study, it was possible to determine the links of the pathogenic unity of dental inflammatory pathology and hematological disease.

The use of complex preparations of natural origin allowed to optimize the treatment of dental pathology. We studied the experience of using a complex biological preparation manufactured at the Department of Pharmaceutical Technology and Organization of Pharmacy at the Azerbaijan Medical University for the treatment of Inflammatory periodontal diseases (IPD), (Eurasian patent No. 036150 dated 05.10.2020) [64].

The investigation involved 50 patients with BTM aged from 13 to 35 years (mean age 16.0 + 0.1 years) with inflammatory diseases of the oral cavity tissues. The first observation group consisted of 18 patients with BTM who received traditional IPD treatment with professional oral hygiene and a biological product of natural origin. The second group consisted of 16 patients with BTM, who were administered a solution of chlorhexidine bigluconate at a dilution of 0.05 % along with professional hygiene treatment for IPD. The control group consisted of 16 patients who followed professional oral hygiene without prescribing antiseptic agents.

The biological medication contains an extract of medicinal plants based on licorice roots, sage leaves, calendula flowers, chicory roots, knotweed herb, creeping thyme, taken at a ratio of 2: 2: 1: 1: 1: 2. Olive oil is used as an extractant at 1:10 ratio of medicinal plants collection to an extractant, by adding chitosan and ascorbic acid.

After a clinical ans OPTG examination, patients of all groups involved in the study, received professional oral hygiene treatment appropriate to the recommendations for individual oral hygiene. In the complex treatment of IPD of the main group, a complex biological medication was prescribed, with the administration of rinsing by an aqueous extract for 5 minutes and application of an oil extract with cotton swabs on the gum tissue, twice a day for 15 minutes, for 2 weeks.

The results of the comparative analysis revealed reliable clinical efficacy of the complex biological preparation in relation to the comparison and control groups. This was manifested by a significant improvement in the indices of gingivitis, bleeding and PHP hygiene index.

The value of the hygiene index (GI) in the main group before treatment was 1.94 ± 0.018 points, and a month after the basic therapy course with herbal preparation, the index values decreased by almost 2.5 times and averaged 0.66 ± 0.025 points ($p < 0.001$).

The study of the gingivitis index (GI) in patients with BTM in the control group, who received traditional treatment without the use of antiseptics, also enabled to establish some positive dynamics in indicators, but to a much less extent than in the other two groups. In the control group, the values of the gingivitis index as a result of treatment in the same period decreased only to 1.09 ± 0.037 points, versus 0.77 ± 0.023 points in the comparison group ($p < 0.001$).

Thus, both in the main and in the comparison groups, an improvement in the indicators of the hygiene index is manifested. But in the main group, the therapeutic effect of the treatment was more pronounced. A comparative statistical analysis of the bleeding index indicators in patients of all three groups revealed that almost half of the subjects were diagnosed with bleeding while brushing their teeth and eating.

Comparative analysis of the bleeding index findings in a month after treatment revealed a decrease in indicators of all study groups, but compared with the control and comparison groups, this indicator was found to be more pronounced in the main group.

After using the complex biological preparation, a month later, bleeding occurred rarely or did not absolutely occur, as evidenced by a sharp decrease in the index of bleeding of the gingival sulcus to 9.3 ± 1.15%. In the control and comparison groups of the examined patients, a different picture emerged. Thus, despite the necessary professional oral hygiene, the obtained index data still indicated the presence of bleeding and clinical signs of moderate gingivitis in the control group. The bleeding index was 21.1 ± 0.99% in the control group and 10.6 ± 1.01% ($p < 0.001$) in the comparison group.

Thus, a moderate form of gingivitis according to the bleeding index was detected in the control group at the final stage of the study, 6 months after treatment.

As a result of the complex therapeutic and prophylactic measures, a pronounced decrease in the values of the PHR hygiene

efficiency index was noted almost equally in all groups of patients with BTM.

The indicators of the hygiene index in all groups did not statistically differ before treatment and after the completion of basic and maintenance therapy course in the main group, the index indicators were lower than in the other groups of observations ($p < 0.01$).In the main group, after a month, the index value was 1.31 ± 0.023 points, and 6 months after the completion of complex therapy, the index value was statistically changed a little and was equal to 1.12 ± 0.038 points. In the control and comparison groups, after the treatment, this indicator was increasing, compared with the data of the previous stage of clinical trials. In group 3, after 3 months, the index indicator was 1.70 ± 0.081 points, and after 6 months, 1.78 ± 0.086 points. In group 2, after 3 months and 6 months, the index value was 1.07 ± 0.048 and 1.78 ± 0.086 points, respectively.

Complex periodontal treatment in the first main group with the application of a biological herbal preparation resulted in a significant decrease in seeding rate of the various types of cariogenic and periodontal pathogenic microorganisms in the mixed oral fluid.

It is important to note that the herbal remedy, due to its biological neutrality, has a selective inhibitory effect to a greater extent on pathogenic microflora than on their resident species. So, the detection frequency of Porphyromonas gingivalis, in this group of BTM patients with periodontal diseases at the end of basic therapy course (a month after treatment) significantly decreased to 1.52 ± 0.08 lg KOE/ml, versus 3.72 ± 0, 24 lg KOE/ml before treatment ($p < 0.05$). At the same time, the contamination of the oral fluid by yeast-like fungi of the genus Candida albicans decreases sharply to 1.27 ± 0.09lg KOE/ml (after 3 months) versus 8.08 ± 0.35 lg KOE/ml before the treatment ($p < 0.05$).

The incidence of fungal infection was also significantly lower than the values before the treatment and at the final stage of bacteriological studies. So, after 6 months, a colony of fungi of the genus Candida was found in the amount of 4.48 ± 0.27 lg KOE/ml in a biological sample taken from the oral cavity.

In the course of treatment, a selective antimicrobial effect of the biological preparation against pathogens was identified with an increased amount of non-pathogenic oral microflora, particularly, Lactobacillus spp. Therefore, one of the factors of the therapeutic effect of the medication is the restoration of normal oral biocinosis. The therapeutic effect of the natural biological preparation was distinguished by a long-term duration lasting for over the next 6 months, in contrast to the short-term effect of using chlorhexidine (within 2-3 weeks).

Orthodontic correction makes a significant contribution to the health improvement of BTM patients as well.

When planning orthodontic treatment, it is necessary to take into account the severity of the deformity, the age of the patient, the sagittal relationship of the jaws, the degree of narrowing of the jaws and the presence of protrusion of the incisors. Depending on the patient's age, we used activators, mechanical, functional, removable and fixed orthodontic techniques. The type of growth of the upper and lower jaws plays an important role in the harmonious shaping of the face during growth. Therefore, we evaluated the effectiveness of the treatment of a dentoalveolar class II of Angle anomaly using the Twin block orthodontic functional device. The Twin block appliance is used to modify the growth of the lower jaw and correct the ratio of the jaws in the sagittal plane. Observations were performed on the patients who did not have any syndromic and systemic diseases and patients with BTM. As a result of the orthodontic treatment, the lower jaw was displaced forward in both groups. Analysis of cephalometric data of patients of 2 groups revealed a significant difference in indicators, pointing out the anteroposterior relationship of the jaws. As a result of impact of orthodontic forces, there was a statistically significant increase in the parameters SNB, Co-Gn, N-ANS, ANS-Me and N-Me, and a decrease in the overjet value. Orthodontic treatment of patients with BBT using the Twin-block appliance at the stage of mixed dentition effectively improves the intermaxillary relationship and the functions of the maxillofacial region.

The result is the restoring the nasal breathing and the optimizing the expiration which can improve the respiratory functions and prevent acute and chronic respiratory diseases and their exacerbations. The function of the epiglottis improves, preventing reflux and aspiration complications due to advanced positional changes in the oral cavity and upper respiratory tract organs.

Optimization of the tongue position affecting the function of swallowing, stimulates the improvement of the gastrointestinal tract organ's state. A noticeable aesthetic effect contributes to the social adaptation of persons who suffer from BTM.

The sum of positive effects is likely to be a good basis to realize the need to introduce orthodontic care as an obligatory part of dental supervision.The positive effect of multifactorial metabolic correction proves the impact of homeostatic disorders in the pathogenesis of multiple pathology in patients with BTM.

Dental diseases, being of infectious-inflammatory, degenerative-dystrophic nature in BTM are characterized by special mechanisms of pathogenesis that differ from ordinary dental diseases.

This allows us to consider dental pathology in patients with BTM as one of the clusters of the multiple organ symptom- complex of this hereditary disease.

Therefore, it is required that approaches to dental treatment of BTM patients should take into consideration the metabolic disorders and must be complex.

CONCLUSIONS

1. The structure of stomatological morbidity of patients with β-thalassemia major changes its priorities with age: up to 12 years old, caries prevails in patients, then inflammatory periodontal diseases are more often recorded. Thus, in the age group of 3-5 years, the CP index was 9.41 ± 0.62; in the group of 6-12 years old, the KPU + kp index was 9.75 ± 0.35; in the 13-17 year old group, the KPU index was 6.84 ± 0.25; in the group over 18 years old - 9.41 ± 0.62 [18.19, 48, 52, 60].

2. The severity of inflammatory periodontal disease and the number of reported cases of periodontal disease in patients with β-thalassemia major increase with age. The average number of healthy periodontal sextants in the 6-12-year-old group was 1.74 ± 0.40, in the 13-17-year-old group - 0.87 ± 0.34, and in the 18-year-old group - 2.75 ± 1.03 [35, 38, 39, 41, 44]. [35, 38, 39, 41, 44].
3. Craniofacial changes in patients with β-thalassemia major indicate the presence of skeletal pathology according to the Angle class II (∠SNA = 79.0 ° ± 0.9, ∠SNB = 72.4 ° ± 0.8, ∠ANB = 6.6 ° ± 0.7) with a decrease in the size of the body of the lower jaw (GoGn = 63.9 ± 1.2 mm). In patients with β-thalassemia major, compared with the control group, a significant decrease in the following parameters was found: tongue length ($p<0.05$), soft palate length PNS –V ($p <0.05$), upper($p <0.05$), middle ($p <0.05$) and lower width ($p <0.01$) upper airways. The hyoid bone in patients with β-thalassemia major is displaced up and back, and is located closer to the lower border of the mandible [4, 37, 40, 42, 43, 50, 54, 57, 65].
4. In the course of anthropometric studies in adult patients with β-thalassemia major, the following were observed: an increase in the head in transverse dimensions, narrowing of the lower jaw, shortening of the growth of the ramus of the lower jaw, flattening of the bridge of the nose, narrowing of the nasal root, orbital hypertelorism, protrusion of the vertical contour of the upper lip. Changes in the soft tissues of the face are more pronounced in comparison with changes in bone parameters [45, 47, 51, 54, 59].
5. Disruption of the bonds of tonofilaments with desmosomal plates in patients with β-thalassemia major along with hypoxia, is the reason for the accumulation of glycogenic granules in the cytoplasm of keratinocytes instead of the keratin matrix, thereby preventing the formation of the stratum corneum of the epithelial covering and causing the occurrence of long-healing gum wounds . [20, 22, 23, 25, 39, 65].

6. Disruption in patients with large β-thalassemia of the bonds of tonofilaments with desmosomal plates, along with hypoxia, is the reason for the accumulation of glycogenic granules in the cytoplasm of keratinocytes instead of the keratin matrix, thereby preventing the formation of the stratum corneum of the epithelial covering, which performs a barrier function, which leads to the development of a dystrophic component in process in periodontal diseases [23, 30, 39, 65].
7. In adult dental patients with β-thalassemia major, a pronounced imbalance in the presence of vital macro and microelements Ca, P, Fe has been established. The level of iron in the blood significantly ($p < 0.001$) exceeded the normal range, being a biochemical substrate of hemosiderosis of organs and tissues as well as , calcium and phosphorus metabolism [29, 31, 32, 38, 41, 44, 46].
8. The established metabolic disorders in the organism of patients with β-thalassemia major support the systemic mechanisms of inflammation, which is confirmed by the high level of cytokines imbalance in the blood: IL-6, IL-10 TNF-α ($p < 0.001$) [29, 31, 34, 39, 44].
9. High dental morbidity associated with multifactorial homeostatic disorders in BTM patients organism requires the complex metabolic correction means for restoration of mineral metabolism balance in cytokine cascades, immunological defense processes and nonspecific reactivity of organism to be included to the dental therapeutic - prophylactic measures. [36, 38, 44, 46, 64].
10. The effectiveness of orthodontic treatment in the prevention of dental morbidity in patients with β-thalassemia major has been stated. The effectiveness of the use of a complex neutral preparation of natural origin in dental patients, in the prevention and treatment of periodontal and oral mucosa diseases has been established, which is confirmed by a decrease in the indices of the bleeding index of the gingival sulcus to $9.3 \pm 1.15\%$, the PHP index to 1.31 ± 0.023 points and the growth of non-pathogenic oral microflora [49, 53, 64].

PRACTICAL RECOMMENDATIONS

1. Patients with β-thalassemia major in the course of dispensary observation are recommended to carry out an annual additional targeted examination to dynamically assess the state of metabolism of iron, calcium, phosphorus; balance of pro - and anti-inflammatory cytokines (TNF-α, IL-6, IL-10, IL-2);
2. It is advisable to include means of metabolic correction with multimodal activity to the program of therapeutic and prophylactic measures for patients with β-thalassemia major;
3. Dental unit at multidisciplinary thalassemia patient care centers should include orthodontic services;
4. In order to improve the efficiency of dental care for BTM patients it is necessary to develop and introduce into healthcare practice new organizational forms of interdisciplinary interaction of dentists with doctors of various specialties including not only hematologists, pediatricians and therapists, but also endocrinologists, clinical immunologists and others.
5. An electron microscopic examination of the biopsy material of the gums using modern computer programs can be considered as one of the safest and most cost-effective methods to determine the iron elements accumulation level in the organism of BTM patients.

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Patents

1. Means for the treatment and prevention of periodontal disease and oral mucosa. Eurasian patent No. 027001 dated June 30, 2017. (co-author R.M. Heydarov, M.N. Veliyeva).

LIST OF USED SHORTNESSES

BTM – β -thalassemia major
TRG – teleradiography of the head
OPTG – orthopantomography
CCSG – chronic catarrhal-sclerosing gingivitis
Sİ – serum iron
TIBC – total iron binding capacity
LIBC – latent iron-binding capacity
% STI – saturation percent of transferrin of iron

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