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Peculiarities of Phosphorine Calcium Exchange in the Pathogenesis of Dental Caries in Children with Diabetes of the First Type

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ABSTRACT
The main purpose.Assessment of caries resistance of hard tissues of the teeth (oral cavity) and the state of phosphoric calcium metabolism in children with type 1 diabetes mellitus, taking into account the mineralizing potential of oral fluid and antimicrobial protection of the oral cavity.
Materials and methods. A general clinical, dental, laboratory examination of 127 children with type 1 diabetes mellitus, aged from 7 to 12 years, with an endocrinopathy experience of eight months to ten years was conducted. The obtained data were compared with the results of a survey of 37 "healthy" and "practically healthy" children of this age category. When assessing the dental status of children, a hygienic index was used (Y. A. Fedorov, V. V.Volodkina, 1970), the EC + kp index (EC- Expert Committee, 1962), the OHI-S simplified hygienic index (Green, Vermillion, 1964).The intensity of the enamel of teeth demineralization processes was assessed by using an enamel resistance test (V. R.Okushko, L. I. Kosareva, 1984), vital staining (coloring) (LA Aksamit, 1978). The electrometry of the hard tissues of the teeth was carried out by the electro-diagnostic apparatus of "Dent Est" (V. K.Leontiev, G. G.Ivanova, 1985). Laboratory diagnosis of salivary parameters included the study of calcium (total ionized), inorganic phosphorus, alkaline phosphatase, osteo-calcine, parathyroid hormone, 25 hydroxy-vitamin D3, lactoferrin. Micro-crystallization and mineralizing potential of the oral fluid were determined according to Leus P. A. (1977).
Results. In the early stages of development of type 1 diabetes, children have a compensated and sub-compensated form of the carious process, an increase in the permeability of the enamel, a slight predominance of demineralization processes in the solid tissues of the teeth over the processes of remineralization, which indicates self-regulation of the mechanisms of mineral metabolism while maintaining physiological re-mineralizing properties of the oral fluid.In the late stages of development of type 1 diabetes mellitus, high intensity and decompensated form of the course of carious lesions, low structural and functional resistance of enamel, expressed processes of demineralization of hard tooth tissues are established. The emergence of this complex in children with an endocrinopathy experience for more than five years indicates the depletion of salivary gland functionality, the violation of mobilization salivary systems in response to the occurrence of a cariogenic situation in the oral cavity, a change in calcium homeostasis, a decrease in enamel resistance to organic acids, saliva to crystallization.
The conclusion. The growing positive dynamics of index growth in children with long-term type 1 diabetes mellitus, indicating a worsening of the dental status, requires adherence to the principles of rational nutrition, quarterly professional dental caries with the use of modern and effective oral care products, the introduction of active forms of hygienic training and education, taking into account the mineralizing potential of oral fluid, as well as careful monitoring acquired manual skills.

Keywords: Children's population, diabetes of type 1, Saliva diagnostics, Mineralization of teeth, Enamel resistance, Calcium homeostasis.

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INTRODUCTION

Diabetes is a noteworthy worldwide issue because of drastically expanding around the world [1]. And, as [2] pointed out Diabetes is a major contributor to the worldwide burden of ailment. A group of widespread metabolic disorders that possess the phenotype of hyperglycemia has been referred to as Diabetes mellitus [3]. The Diabetes (D) of type 1 is the immune-mediated, chronic multifactorial

disease with the subclinical period which is caused by the progressing destruction of insular β-cells of a pancreas which results in the absolute deficiency of insulin [4]. By experts it is established that various auto antibodies to insular β-cages, defined at 86 – 98% of children for the first time, they revealed that endocrinopathy is the specific marker of this pathological process [5,6].

The created regional and national registers of Diabetes of type 1 in children and teenagers have confirmed the broad variability and prevalence of an endocrinopathy, depending on the population and geographic latitude worldwide (7 – 40 cases in 100 thousand children a year). According to the International diabetic federation (International Diabetes Federation, IDF), for the last two decades the incidence of Diabetes of type 1 among children has tended to continuously increase. By the beginning of 2011, there were found 479,6 thousand children with Diabetes of type 1, a quarter of these patients was in the age category up to four years, and the number for the first time of the revealed cases was 75 800 [7].

In the Russian Federation on the period of 1.1.2011, according to the State register, 17 519 children have been registered with Diabetes of type 1, that among them 2911 cases were diagnosed for the first time, and the average indicator of the incidence of the Diabetes (D) of type 1 in children's population was 11,2 per 100 thousand [8].

In pediatrics, Diabetes of 1 type is one of the most widespread metabolic and endocrine states, and about 80% of all cases of the endocrine pathology has been diagnosed during the periods of intensive growth (4-6 years, 8-12 years, the pubertal period) (American Diabetes Association (ADA), 2017; European Association for the Study of Diabetes (EASD), 2015). In the absence of the replacement lifelong therapy by insulin, in patients with Diabetes of type 1, the violations of all types of metabolism would cause a lethal outcome owing to ketoacidosis or ketoacidosis's coma. The peculiarities of Diabetes of type 1 in children include the complexity in the achievement of the compensation of carbohydrate exchange, and the expressed lability of a glycemia, and tendency to develop the autoimmune reactions which are combined with the increased reactivity of the immune system [9-11].

In most of the children suffering from Diabetes of type 1, the loss of insulin producing β-cells of the pancreas is the result of autoimmune damage to the insular device. Among the most diagnostic significant markers of an autoimmune insulin, the experts have allocated antibodies to tyrosine phosphatase (Insulinoma-Antigen – to IA-2α), a glutamate deccarboxylase (Glutamate Decarboxylase – GAD), and also to cytoplasmic antigen (Islet Cell Antibodies – ICA). The key place in the pathogenesis of Diabetes of type 1, on an equal basis with antibodies to antigens of the insular device of a pancreas, is occupied by the antibodies to insulin (Insulin Autoantibody – IAA). These antibodies, unlike other epitops of the antibodies to insulin are antibody makers which produce the secretion of β-cages, therefore they can be revealed on the preclinical (asymptomatic) period of a disease in children of younger age categories [12]. Researchers have established close interrelation of _AA with the other pro-diabetic antibodies (to IA-2α, GAD, ICA). It is important to note that the irrespective of the genetic predisposition, the most considerable prevalence of the autoimmunity against the insular antigens and insulin has been revealed in territories with the high incidence of Diabetes of type 1 [13,14].

More essential frequency of the identification of IAA in children of the younger age groups in comparison with the senior age categories experts can be explained by the considerable aggression of the autoimmune process due to the presence of the communications with the immunogenic markers. Besides, the type of feeding of the child aged up to one year is important. Replacement of breastfeeding on artificial, especially with the use of mixes on the basis of cow's milk because of the expressed anti-gene stimulation and the development of the cross reactions to insulin and animal protein, with the genetic predisposition creates prerequisites for hyper production of IAA [15].

In a small number of patients, the signs of the autoimmune process have been absent, however the symptomatology of the absolute deficiency of insulin has been observed. In such cases, when the etiology of destruction of β-cages and an insulinpeniya has been unknown, it was accepted to speak about the idiopathic option of Diabetes of type 1. Despite the similarity of a clinical picture, this disease is not of the autoimmune nature, but auto-antibodies and genetic markers of Diabetes of type 1 at the same time have not been found [16].

According to the modern scientific data, the development of the carious process is caused by the difficult interaction of the local and general factors which are implemented in the "cariogenic microflora-oral liquid-enamel resistance" system [17]. The violation of the structure (properties) of oral liquid belongs to the most significant local risk factors of the emergence of the carious process, except for the cariogenic microorganisms [18-21]. The

stability of the oral liquid representing ion-proteinaceous true solution, provides the integration of solid and soft fabrics into oral cavities and also normal activity of the bodies of an oral cavity of a mouth and an organism in general. The oral liquid as a functional unit and the indicator of work of a gemato-salivary barrier takes active part in the maintenance of a homeostasis of the inner environment and first of all – the blood. The mineralization factors (organic and inorganic substances, vitamins, hormones) which are contained in the oral liquid, provide the processes of maturing of enamel and the resistance of the solid tissues of teeth. Ions of calcium and phosphates as basic elements of hydroxyapatites of enamel carry out the mineralizing function of the mixed saliva, and calcium level in the oral liquid is twice less than in blood, because of the connections with mucin (micelles). In the oral liquid, calcium is in the ionized form (50%), in connections with proteins (15%), and in connections with citrates and phosphates (35%). The general level of calcium in the oral liquid approaches its level in blood serum and the content of the serosity ionized calcium exceeds salivary, and the concentration of calcium in oral liquid directly depends on pH level. The shift of pH towards acidosis reduces the mineralizing potential of the oral liquid causing its calcium imbalance. The optimal indicators of pH at which the oral liquid is oversaturated by the ions of phosphorus calcium, and performs the mineralizing function; as a result, there would be neutral or poorly alkaline environment [22-24]. The level of the ionized calcium in the oral liquid has direct correlation depending on the salivation speed. It has been also important to note the role of a mucin in the maintenance of a phosphorus-calcium homeostasis. The maintenance of the buffer properties of the oral liquid is provided due to the formation of the denatured organic film adsorbed on the surface of the teeth insoluble consisting of complex connections of a mucin with the ions of phosphorus and calcium [25,26].

The stable salivation provides effective removal (ekzo) endogenous microorganisms and their metabolites, the maintenance of the homeostatic balance in the oral cavities and also the steady presence of the specific and nonspecific protective factors [27-29]. The lactoferrin is indirectly involved in the processes of the cellular immunity, and is related to the system of the congenital immunity representing the multifunctional protein and having the iron-binding ability. Besides, the biological role of a lactoferrin consists in the anti-inflammatory, antiviral, antifungal, antibacterial, anti-parasitic, and catalytic activities; also its antineoplastic and enzymatic properties have been proven [30].

Despite a large number of the works done by the domestic and foreign experts devoted to studying the mineralizing potential of the oral liquid on a calcic homeostasis, the researches revealing the early violations of phosphorus-calcium exchange in the children suffering from Diabetes of type 1 are rare. There have been no systematization of the laboratory and diagnostic data establishing the interrelation of the enamel resistance and markers of a mineralization in the oral liquid in children with the various experiences of Diabetes of type 1. There have also been no results on studying the level of lactoferrin in the oral liquid in children with various durations of Diabetes of type 1, and also there have been no data on the condition of the anti-microbe protection of an oral cavity and the communication of the maintenance of lactoferrin with the resistance level to caries in children with endocrinopathy. In this regard, studying calcium - phosphorus exchange and calcium - the regulating hormones in oral liquid, the features of micro-crystallization of the mixed saliva, anti-microbic protection of the oral cavity in children with Diabetes of type 1 would allow to improve the donozological diagnostics of the violations of the mineral exchange and also reveal the critical periods of the decrease in the anti-microbe protection of an oral cavity in the various terms of development of endocrinopathy. It is important to note that the researches on the pathophysiological mechanisms of the formation, development of the carious damages of teeth in children with Diabetes of type1 taking into account the mineralizing potential and the level of a lactoferrin in the oral liquid have been relevant, and of reasonable interest not only of the scientists, but also of the practicing experts. The introduction of the received results would allow improving the available means of the local and general pathogenetic prevention of the carious defeats in children with different levels of the resistance to caries.

The purpose of the research

was to assess the caries-resistance of the solid tissues of teeth and a condition of phosphorus-calcium exchange in children with diabetes of the first type, taking into account the mineralizing potentials of the oral liquid and the anti-microbe protection of the oral cavity.

MATERIALS AND METHODS OF THE RESEARCH

This research on the children conformed to the ethical standards of the bioethical committee

which have been developed according to the following international and Russian normative legal acts: The Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964) "Ethical principles of carrying out a scientific medical research with participation of the person" with amendments LXIV to the General Assembly of WMA (2013); Art. 24 of the Constitution of the Russian Federation; "Rules of clinical practice in the Russian Federation" (Order of the Russian Ministry of Health No. 266 from 6/19/2003); ethical standards of Committee on experiments, standards of performing clinical trials (GOST P 52379-2005). On carrying out all types of the studies, a voluntary informed consent was received from the parents (trustees).

While performing the work, all the clinical, laboratory, radiological examination of 127 children suffering from Diabetes of 1 type aged from 7 up to 12 years who were on the treatment in the endocrinological hospital of «Children's City Clinical Hospital " in Krasnodar and "Children's City Clinical Hospital of G.K. Filippsky" in Stavropol were conducted. The endocrinopathy duration in children with the diagnosis of "Diabetes of type 1 " was from eight months to ten years. Children with Diabetes of type 1 were hospitalized in a hospital in a de-compensational phase, and had no accompanying pathology (congenital, autoimmune, infectious) which could complicate the interpretation of the results. The diagnosis of "Diabetes of type 1 " was established by the results of the laboratory experiments (the general blood test; biochemical blood test with the determination of the level of glucose; the analysis of urine) and also all the clinical inspections were done according to the criteria of WHO (World Organization of Health) (1999). For establishment of the extent of the metabolic compensation of carbohydrate exchange, the level of glycemic hemoglobin (HbA1c), and by S-peptide secretion – residual function of β-cells of a pancreas were determined. Taking endocrinopathy duration into account, all the sick children were divided into three groups: the 1st group – the duration of Diabetes of type 1 till 1 year (n=38; 29,9%); the 2nd group – the experience of Diabetes of type 1 from 1 year to 5 years (n=44; 34,6%); the 3rd group – the duration of Diabetes of type 1 from 5 to 10 years (n=45; 35,5%). The group of the comparison has made 37 healthy children who were also divided into 2 groups: "healthy – the I group of health" and "almost healthy – the II group of health" children (Yu. E. Veltishchev, 1994) in the same age category. The diagnosis was made by a pediatrician considering the results of the laboratory experiments and the all-clinical status.

The assessment of the dental status was carried out on the basis of the departments of the stomatology of the general practice and the children's stomatology of SSMU (Stavropol State Medical University) and the department of the children's stomatology, orthodontics and maxillofacial surgery of KSMU (Kuban State Medical University). When studying the dental status in children in the period of early (7-9 years) and late (9-12 years), the following indexes were used: the hygienic index (HI) (Yu.A. Fedorov, V.V. Volodkina, 1970) – for the definition of the condition of hygiene of the oral cavity; the KPU+ index of rc (committee of WOH experts, 1962) – for the identification of the degree of prevalence of teeth caries; the simplified hygienic OHI-S index (Green, Vermillion, 1964) – for determination of the surface area of the tooth covered with a dental plaque). The activity of the caries was estimated according to the classification (1972) (tab. 1) by T.F. Vinogradova.

Table 1. Activity of caries of teeth (Vinogradova T.F., 1972), (points)

Age	Indexes	I degree (compen sated)	II degree (subcompen sated)	III degree (decompen sated)
3-6	CE	Less than 3	3-6	More than 6
7-10	CE+ce	Less than 5	6-8	More than 8
11-14	CE	Less than 4	5-8	More than 8
15-18	CE	Less than 7	7-9	More than 9

The expressiveness of the processes of the demineralization of enamel of teeth was assessed by the test of the enamel resistance (TER) and on the condition of the mineralizing saliva's potential. The TER-test (V.R. Okushko, L.I. Kosareva, 1984) was applied to study the structurally functional resistance of the tooth enamel and its acid- resistance. For the assessment of the intensity of the coloring thee, a (specific) ten level scale of the blue color paper with the gradation of the color saturation from 10% to 100% was used. The assessments of the results included: the enamel of the teeth steady against the acid factors – the intensity of coloring up to 30%; enamel of teeth, the middle resistance to the effects of acids – the intensity of coloring from 30 to 60%; enamel of teeth which was not steady against the effects of acids – the intensity of coloring from 60 to 100%.

By the method of vital coloring, the diagnostics of the focal demineralization of enamel (L.A. Aksamit., 1978) was performed with the use of "Caries indicator" (Company: Omega Dent, Russia). The intensively, or poorly painted over

sites of the tooth enamel were interpreted as demineralized ("positive test"), the healthy enamel was characterized by the lack of coloring ("the negative test"). In the analysis of the intensity of coloring of enamel (ICE), a color standard scale was applied with the various shades of blue color (from slightly bluish to dark blue). The results were estimated in points (from 1 to 10). The assessments of the results were as following: if the activity of the demineralization was low –the intensity of coloring of the centers would be up to 3 points; for the activity of demineralization of an average degree – the intensity of the coloring of the centers would be from 3 to 6 points; and for the high activity of the centers of the demineralization – the intensity of the coloring would be from 6 to 10 points.

In order to increase the informational content of the identification of the focal demineralization of enamel, the electrometry of the solid tissues of tooth (ESTT) with the use of the electrodiagnostic device "Dent Est" ("Geosoft Dent", Russia) by the methodic of V.K was also used (Leontyev's , G.G. Ivanova, 1985). The mirror (a passive electrode) was fixed on the soft tissues of an oral cavity (a cheek, a lip), and the end of the active electrode (the syringe from 10% calcium chloride solution) moistened with the electrolyte was established on the explored site of the tooth and its motionless state was controlled when carrying out the measurements. The measurement of the sizes of each tooth was carried out in three different points, and for calculations, the worst (maximum) values were used. The interpretation of the sizes of the electrometric diagnostics was carried out according to the recommendations of (Leontyev V.K., Ivanova G. G., 1985) (tab. 2).

Table 2. Interpretation of sizes of the electrometric diagnostics of the solid tissues of teeth (Leontyev V.K., Ivanova G. G., 1985), (points)

Size of current, (mk)	Preliminary diagnosis
Less than 0,2	Mineralized intact enamel
0,3 – 3,9	Precarious condition of enamel
4,0 – 7,9	Initial caries
8,0 – 27,9	Superficial caries
28,0 – 50,0	Average caries
More than 50	Deep caries

Interpretation of the values of the electrometric diagnostics of hard tissues of teeth

The subject of the laboratory diagnostic testing was not the stimulated oral liquid (NSOL). The fence of NSOL was carried out in the morning (from 8 to 9 o'clock) on an empty stomach till the night to the tooth brushing, after preliminary rinsing of an oral cavity with the help of the distilled water (20-24 C°) by means of the special system for collecting Saliva RNA Collection and Preservation Devices saliva ("Norgen Biotek", Canada). The collected NSOL was centrifuged at 8000 whirls per minute within 15 minutes. After that, a sludge part of NSOL was spilled on alikvote on 200-250 ml in plastic test tubes and stored in the frozen state at t=-76ºC prior to the research. The received biomaterial within an hour was transported in to the different places: The office of the laboratory diagnostics of "Stavropol Regional Clinical Consulting and Diagnostic Center", the laboratory of the department of the medical biochemistry, the clinical laboratory diagnostics, and the pharmacy of the Institute of NCFU (North Caucasus Federal University), the department of live systems and the clinical-diagnostic laboratory, and "Stavropol regional clinical hospital".

The quantitative definition of a lactoferrin (LF) to NSOL was carried out by the method of the solid-phase immune-fermental analysis (IFA) with the use of set of Varnish — a Toferrin-strip reagents of “Vector-Best” (Russia).

The research in NSOL on the level of calcium, phosphorus, and the activity of the alkaline phosphatase (AP) was conducted with use of the ready sets of the instruments for the diagnosis of a company: “Vital Diagnostics” (St. Petersburg). The optical density was measured on the spectrophotometer Federation Council-56 "experimental design bureau the Range" (St. Petersburg). Level 25 of D3, PTG hydroxyvitamin and an osteokaltsin in NSOL were defined on the completely automated immune-fermentable analyzer of Personal LAB ("Adaltis", Italy) with the use of ready sets of reactants 25-Hydroxy Vitamin D EIA, DRG PTH Intact (EIA-3645) and N-MID Osteocalcin ELISA.

The method of determination of the speed of salivation was the following: the child was seated, asked to hang the head and sit in such situation, not to swallow the saliva, not to move the tongue and lips during the entire period of collecting saliva. After the accumulation of saliva in an oral cavity within two minutes, the child was asked to spit out all the contents in a reception vessel. The procedure of collecting was carried out by two more times, so that the general time of collecting was six minutes. The speed of the salivation (ml/min.) paid off as the total amount of the collected saliva divided into the time (six minutes). The definition of a hydrogen indicator pH was carried out by means of the automatic ion-selective analyzer "Easy Lyte Plus" ("Medica Corporation", the

USA). The measurement of the potential of each electrode was carried out in relation to the fixed potential of a double chlorsilver electrode.

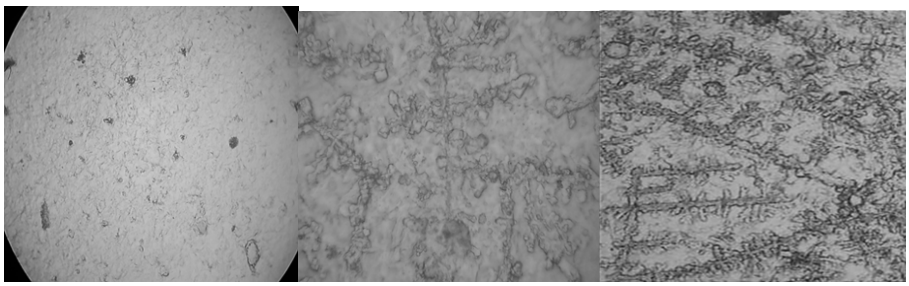
The micro-crystallization of the oral liquid was investigated by the method of microscopy of the dried drop (Leus P.A., 1977, Puzilova O.Yu. modification., Suntsov V.G., 1999). For this purpose, the oral liquid was collected from the bottom of a mouth by the pipette 0,2-0,3 ml of the oral liquid, three of its drops were applied on the sterile subject glass, dried up within two hours in air at °C t=24-25. Further, the dried drops of the oral liquid were investigated by means of a binocular stereo of a pancreas microscope of "MSPE-1" (Russia) in the reflected light with the side and vertical shadow less lighting at increase (×40 – ×400). The analysis of the image of the crystals diagrams was displayed to the monitor by means of the video of an eyepiece DCM-510 combined with the software for processing the images "Scope Photo".

For the purpose of the determination of the mineralizing potential of the saliva, the assessment of the crystals diagrams was carried out at increase (×40). The Mineralizing Saliva Potential (MSP) was defined on Leus P.A. (1977): 1 point – a scattering of the chaotically located structures of the irregular shape; 2 points – a thin grid of lines on all field of the vision; 3 points – separate crystals of the irregular shape against the background of the hills and grids; 4 points – treelike crystals of the average sizes; 5 points – the accurate, large crystal structure similar to a fern or a parquet. Then, each of three drops of oral liquid was estimated, and the average size of Ministry of Railways: 0-1 – very low; 1,1-2,0 – low; 2,1-3,0 – satisfactory; 3,1 - 4,0 – high; 4,1-5,0 – very high, was counted.

By results of studying the monocrystal of the oral liquid at increase ×400, the morphological features on which the summation points have been appropriated, were created. Taking the set of quantitative and qualitative morphological features into account, three types of micro-crystallization of the oral liquid were allocated. The first type (30 and more points) – the large, extended cristal- treelike structures with the accurate drawing, correctly accreted among themselves with the formation of "horsetail" or "fern". The crystal structures were located on the relation to each other at an acute angle in the range of 30-45 °. The multiple affiliated branches were departed from a maternal matrix strictly at the right angle. A crystal lattice thin and "gentle" that was the reflection of the physical and chemical properties of the oral liquid, particularly the saturation minerals, was an indicator of viscosity. The centers of crystallization (fig. 1) were revealed. The second type (from 15 to 30 points) – had single crystal-looking conglomerates or crystal-prizma structures which were thinner than the size of the crystals of the first type. The crystals located in the central area were more indistinct, the number of the affiliated branches was lowered, and at the same time, the shoots were shorter, also the tilt angle in relation to the maternal was more variable. The decrease in the number of the structures and their blurring was an indirect sign of the reduction of the viscosity, the lowering level of the by calcium and other elements, the reduction of the mineralizing potential of the oral liquid (fig. 2). The third type (14 points and less) – a large number was isometric, and the small crystal structures were separately located in the form of a rod or a branch, and also the crystals of star-shaped, rounded and irregular shape without orientation were observed. The conglomerates of a cross-shaped form were also separately located, or the total absence of crystals was observed demonstrating the minimum quantity of the minerals (fig. 3). The cariogenic situation of an oral cavity objectively reflected three types of the micro crystallization.

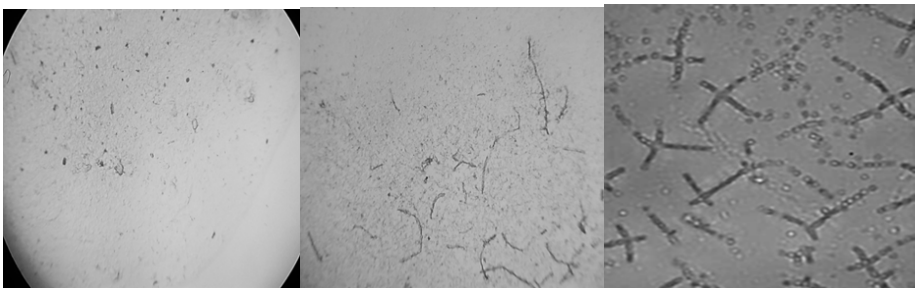
a b c

Picture 1. First type of micro crystallization of oral liquid (a-increase 40; b – increase of 200; c – increase of 400)



a b c

Picture 2. The second type of micro crystallization of oral fluid(a – increase of 40; b – increase of 200; c – increase of 400)



a b c

Picture 3. The third type of micro crystallization of oral fluid(a – increase of 40; b – increase of 200; c – increase of 400)

The obtained laboratory and diagnostic and clinical data were processed by the methods of the variation statistics on Fisher R.A. (2006) by means of the applied software package of StatPlusV25. At the description of the quantitative signs, the average size (M), and a standard error of average (m) were applied. At the assessment of the differences of the categorical variables in groups, an exact method of Fischer or χ2 was used. Statistical data processing was carried out by the methods of the descriptive statistics, the methods of the dispersive analysis (criterion Styyudent's t-criterion), the correlation analysis (pair coefficients of correlation of Pearson, Spirmen) and also the methods of the nonparametric statistics (Mann-Whitney and Vilkokson's criterion). Statistically it was taken the reliable considered distinctions in which the probability of a possible mistake was less than 5% (r⍰0,05).

THE RESULTS OF A RESEARCH AND DISCUSSION

The index assessment of the hygienic condition of the oral cavity in children of the studied groups has been presented in tab. 3.

Table 3. The index assessment of the hygienic condition of the oral cavity in children of the studied groups, (M±m), (points)

Indexes	Indexes of Group of researches			
	Group of comparison , n=37	First group, n=38	Second group, n=44	Third group, n=45
IG	1,24±0,11	1,67±0,14*	2,16±0,23*	2,43±0,19*
CFT+c/p	1,97±0,43	2,69±0,87*	4,18±1,14*	6,34±1,35*
OHI-S	1,37±0,12	1,71±0,14*	1,96±0,21*	2,34±0,17*

Note. * – r⍰0,05 it is statistically reliable in comparison with indicators of patients of group of comparison (Nyyumena-Keyls's criterion, Dunn's criterion).

The analysis of the assessment of a hygienic condition of an oral cavity in the children suffering from Diabetes of type 1 demonstrated that at increase in the duration and severity of the endocrine pathology increased the intensity of the carious defeats to "high" and "very high" level is noted at "unsatisfactory" (insufficient) hygiene. According to this study, the change of a hygienic state with "good" – in healthy children on "satisfactory" – in the children with an experience of D of type1 about one year, and

"unsatisfactory" – in the children with an endocrinopathy experience from 1 year to 5 years and from 5 to 10 years was connected with the difficulty of the full-fledged hygiene because of the deterioration in the physical health, the change in the food allowance with the prevalence of the highly carbohydrate food, the painful feelings when holding the individual hygienic actions, the high content of glucose in saliva and also the decrease in the buffer capacity of saliva and alkaline reserves of an organism.

The indicators of the carries' resisting and focal demineralization of teeth in the children of the studied groups have been presented in tab. 4.

Table 4. Indicators of the carries' resisting and focal demineralization of teeth at children of the studied groups, (M±m)

Indicators	Groups of researches			
	Group of comparison , n=37	First group, n=38	Second group , n=44	Third group, n=45
TER-test %	13,17±0,46	19,93±0,82*	30,46±1,08*	51,74±1,46*
Intensity of coloring enamels, points	1,26±0,03	1,85±0,09*	2,77±0,13*	5,62±0,27*
Conductivity tissues of tooth, m/k A	0,26±0,08	1,74±0,67*	2,41±0,79*	3,87±0,98*

Note. * – r⍰0,05 it is statistically reliable in comparison with indicators of patients of group of comparison (Nyyumena-Keyls's criterion, Dunn's criterion).

The systematization of the data of the assessment of the dental status of children with D of type 1 allowed to claim that with an increase in the experience and severity of endocrinopathy, the intensity of the carious process would be increased, and the processes of the demineralization of the solid tissues of teeth was recorded that was confirmed by the decrease in the structurally functional enamel resistance, and the increase in the indicators of the conductivity and also the high intensity of enamel coloring. So, in the children having Diabetes of type 1 about one year (the CFT (caries filling of the teeth)+ the index of c/p (caries process) on the group 2,69±0,87; TER-test – 19,93±0,82%; IOE – 1,85±0,09; ETTZ – 1,74±0,67мкА) was noted as the "low" intensity of the carious process at the "high" acid resistance of enamel. In the children with the experience of having endocrinopathy from 1 year to 5 years (the CFT+ index of c/p on group 4,18±1,14; TER-test – 30,46±1,08%; IOE – 2,77±0,13; ETTZ – 2,41±0,79mr/A), the "average" intensity of carious process was revealed, which was combined with the "moderate" acid resistance of enamel. In the children with the experience of D of type1 from 5 to 10 years (the CFT+ index of c/p on group 6,34±1,35; TER-test – 51,74±1,46%; IOE – 5,62±0,27; ETTZ – 3,87±0,98мкА) the "high" intensity of the carious process at the "low" enamel acid resistance was established. Thus, at the early stages of the development of D of type 1 in children, the compensated and sub-compensated form of a course of the carious process, the increase in enamel permeability caused by the decrease in the formation of ftorapatit and also the insignificant prevalence in the solid tissues of teeth in the processes of the demineralization over the remineralization processes was recorded. According to this study, the clinical regularities caused by the possibility of the self-control of the mineral exchange in the oral cavity against the background of the compensation of the carious process indicate the preservation of the physiological processes of the remineralization of enamel in children with the short experience of endocrinopathy. The structure of the index of intensity of caries (c/p CFT+) in the sick children of the first and second groups showed a rather safe situation –the excess of the number of the sealed-up teeth over the carious. In the children having an experience of D of type 1 for more than five years, the decompensation of carbohydrate exchange, the decompensated form of the carious defeats, the low structurally functional enamel resistance in the expressed processes of the demineralization of the solid tissues of teeth were noted. The insignificant enamel resistance in sick children of the third group had no opportunity to resist to the complex cariogenic (the general, local) factors; to the total defeat of β-cells of islets of Langerhans of a pancreas; to the plentiful adjournment of the mineralized dental plaque; to the transit updating of the mouth considering both the aggressive character of pathogenic and opportunistic microflora; the frequent metabolic decompensation; the hyper-salivation; the decrease in the mineralizing saliva potential; and the insufficient level of rendering the dental help.

The state of calcium - phosphorus exchange and parameters calcium - and the regulating hormones in the oral liquid in the children of the studied groups have been presented in tab. 5.

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Table 5. The state of calcium-phosphorus metabolism and parameters of calcium-regulating hormones in blood serum in children of the studied groups, (M±m)

Indicators, units	Reference measurements	Group of researches			
		Group of comparisons, n=37	First group, n=38	Second group, n=44	Third group, n=45
General Ca, mmol/l	0,75-3,00	0,76± 0,04	0,78± 0,03*	0,91± 0,06*	1,04± 0,02*
Ionized Ca, mmol/l	0,5-0,8	0,56± 0,02	0,55± 0,04*	0,63± 0,05*	0,74± 0,07*
Inorganic P, mmol/l	1,23-5,07	2,98± 0,13	3,54± 0,19*	2,82± 0,07*	4,53± 0,14*
Balance of Ca general/P	0,18-0,25	0,25	0,22	0,32	0,23
General alkaline phosphatase, unit/l	53,0-65,0	47,81± 7,26	58,36± 6,74*	24,69± 2,48*	11,43± 3,39*
Osteocalcin, ng/ml	4,5-6,5	4,53± 0,47	4,97± 0,33*	3,09± 0,19*	2,73± 0,11*
Parathormon, ng/ml	3,5-7,0	6,27± 1,18	12,73± 0,56*	15,42± 2,03*	21,31± 1,27*
25 gidrocsi-D3 vitamin, nmol/l	51,0-64,0	58,62± 4,13	42,37± 4,72*	30,06± 3,04*	13,96± 2,21*

Note. * – r⍰0,05 it is statistically reliable in comparison with indicators of patients of group of comparison (Nyyumena-Keyls's criterion, Dunn's criterion)

The results of the studies on the salivary indicators of calcium - phosphorus exchange and calcium- regulating hormones in the children with D of type 1 have revealed the statistically significant multidirectional dynamics of the changes made by the increase in the endocrine pathology. With increase in the duration of the endocrinopathy, the gain of the level of the general (Ca), the ionized calcium (Ca 2+), the inorganic phosphorus (R) within the average intervals were observed. The chemical features of calcium (rather small atomic radius, presence of two valences) have predetermined the dominant position of calcium in the competition to the other connections and metals at all stages of phosphorus-calcium metabolism. The high biological activity of calcium at the expense of the osmotic pressure and the ionic balance provides the maintenance of a homeostasis of the oral liquid. Besides, calcium is a part of hydroxyapatites of tooth enamel, which increases the resistance of enamel of teeth to the effect of acids by replacing the composition of the apatite of hydroxyl groups, participates in the formation of the crystal structure of the tooth enamel, inhibits the opportunistic and pathogenic microbic flora of the oral cavity, and promotes the apatite sludge from saliva. Thereof, Ca2 + interacts with negatively charged groups of proteinaceous molecules, and the stability of the formed communications has been defined by the level of pH: alkalosis leads to an increase in the negative charge of the molecule of protein and the reduction of the ionized calcium; acidosis leads to the reduction of a negative charge of the molecule of protein and an increase in free calcium. The achievement of the contents Ca2+ as the most biologically active and homeostatic adjustable fraction, to the maximum limit of the physiological norm, confirmed an active phase of carious process. In the children with an experience of D of type 1 for 5 years and more, the increase in the Ca2 level + in NSOL was noted due to the violation of the balance of homeostatic balance on calcium that was caused by strengthening the permeability of calcium through a gemato-salivary barrier, the reduction in saliva calcium of the connected protein, and also the loss of ions of calcium from the enamel of teeth. An exit of the ionized calcium from the apatites of tooth enamel in the mixed saliva was initiated by the protons of the organic acids which was formed in a dental raid of the easily

fermented carbohydrates. According to the researchers' opinion, a calcium level gain (the general, ionized) at the fluctuations of Ca/R in the ratio of NSOL in the children with the long experience of D of type 1 was predetermined by the following factors. First of all, the hypoglycemic symptoms reflected the dysfunction of insulin-producing β-cells of islets of Langerhans of a pancreas in the period of the preclinical stage of D of type 1 provoked the increased desire to eat high-calorific carbohydrate food in the children thereby, supporting the high level of calcium.

Secondly, the increase in the general microbic weight, the expansion of the surface of microbic colonization, the vegetation of the associations of the opportunistic bacteria with the prevalence of the contamination of yeast-like fungi of the sort Candida and hemolytic streptococcus, the considerable strengthening of the pathogenic activity of the cariogenic microflora, significantly increased the concentration of the organic acids, at the same time reduced the activity of buffer (hydro carbonate, phosphatase, proteinaceous) systems and the protective, cleaning saliva function. The total action of pathogenetic factors reduced the salivary mineralizing potential, strengthened the action of the demineralizing acid agents, changed the structure, physical and chemical composition of the saliva, accelerated the dissolution of the main mineral components of hydroxyapatites, and provoked an exit of Ca2 + from the tooth enamel. The progressing decrease of the activity of the bone isoenzyme of AF (alkaline ferment) was increased in an experience of D of type 1 in the children reached to the critical sizes in NSOL already at endocrinopathy duration over 1 year was testified to the tension of the mechanisms' regulating mineral exchange. From this point of view, in the conditions of the mismatch of the homeostatic regulatory mechanisms, AF carries out not only had a role of hydrolysis of the organic phosphates, but also the initiator of the processes of the calcification. The participation of AF in the processes of remineralization of the solid tissues of teeth was carried out due to the potentiation of the binding of phosphates and the ionized calcium on the surface of the tooth enamel, their subsequent accumulation in the optimum concentration and also strengthening the stability of the micellar structures of saliva. In the children with an experience of D of type 1 more than 5 years, NSOL critical decrease of the activity of AF was noted that indicated the acceleration of the processes of the demineralization of enamel due to the impossibility of the further release of the phosphates necessary for the maintenance of the saturated solution of saliva by the mineral components.

As a result of researching the hormones and mediators regulating phosphorus-calcium exchange, it was established that the increase in the duration of an endocrinopathy in the children, NSOL decreased the level of an osteocaltsin, and the 25th D3 hydroxy-vitamin was revealed at the hyper-production of a parat-hormone. The decrease in the contents in NSOL of an osteocaltsin as a sensitive marker of the formation of a bone tissue, according to this research, was caused by the deficiency of the synthesis of it calcium of the connecting protein that indicated the insufficiency of the processes of the bone remodeling at the late stages of the development of D of type 1. The hyper-production of a parat-hormone in the children having more than 1 year mobilization of phosphorus and calcium formed a bone tissue for the maintenance of the optimum level of calcium in saliva with an endocrinopathy experience and also the deficiency of level 25 of D3 hydroxy-vitamin. The essential delay of the synthetic processes in the solid tissues of the teeth in the children with a long current of D of type 1 was confirmed on one hand, by the decrease in the level of osteocaltsin in NSOL, the reduction of the activity of the bone isoenzyme of AF from the other hand – the hyper-production of the parat-hormone indicated the strengthening of the processes of osteoporosis and demineralization.

The maintenance of lactoferrin in the oral liquid of the children of the studied groups has been presented in tab. 6.

Table 6. The content of lactoferrin in the mouth fluid of the children in the study groups, (M ± m), (mkg/ml)

Groups of researches			
Group of comparison, n=37	First group, n=38	Second group, n=44	Third group, n=45
0,87±0,06	1,34±0,11*	1,76±0,09*	1,17±0,03*

Note. * – r⍰0,05 it is statistically reliable in comparison with indicators of patients of group of comparison (Nyyumena-Keyls's criterion, Dunn's criterion)

The mechanism of the antibacterial activity of LF was the most studied. The antibacterial effect of LF was caused by its ability of binding and deducing iron in the connected states in the acidic environment, exhausting, and at the same time, habituating the microorganisms and breaking their cellular metabolism. The LF bactericidal properties were caused as well by the existence of lactoferrinical specific receptors

in the cellular surface of the microorganisms. While contacting with lipo-polysaccharide of the bacterial walls, LF and the oxidized form of iron which was its part, initiated their peroxide oxidation that led to the change of the membrane permeability with the subsequent lysis of cages. The second way of the antibacterial activity (bactericidal effect) which did not depend on the iron-binding ability of LF was carried out by the direct specific interaction of LF and a lipopolysaccharide of a microbic wall, causing the violation of the transport function of the cellular membrane and the osmotic damage of the cage. The LF bactericidal properties were proved concerning the gram-positive and gram-negative microorganisms.

The progressive increase of the LF level correlating with the increase in the intensity, and the prevalence of the carious damages of the teeth in the children with an experience of D of type 1 about one year, and from 1 year to 5 years, indicated the activation of the mechanisms of the antibacterial activity of LF in the process of increase in the clinical manifestations of the endocrinopathy, and the structure-functional destructive changes of the insulin-productive β-cells of islets of Langerhans of the pancreas. The essential lowering of the level of LF as the inflammation marker in the oral cavity, and the indicator of the adverse course of the carious damages of teeth in the children having endocrine pathology more than 5 years, confirmed the exhaustion of the protective and adaptive homeostatic mechanisms, and the development of the irreversible destructive changes in β-insular cells of the pancreas, creating, thereby, prerequisiting of the synchronization of the inflammatory processes in the mouth.

Results of studying of biophysical indicators and the mineralizing potential of oral liquid at children of the studied groups are presented in tab. 7.

Table 7. Condition of biophysical indicators and the mineralizing potential of oral liquid at children of the studied groups, (M±m)

Indicators, Units of measurements	Group of researches			
	Group of comparison, n=37	First group, n=38	Second group, n=44	Third group, n=45
Speed of salivations, ml/min	0,57±0,05	0,51±0,09*	0,43±0,06*	0,31±0,04*
Level of pH, units	7,09±0,11	6,81±0,14*	6,57±0,05*	6,31±0,07*
Mineralizing potential, points	2,74±0,12	2,43±0,17*	1,88±0,09*	1,39±0,04*
Frequency of occurrence of types of microcrystals, %	**I** – 62,1 **II** – 37,9 **III** – 0	**I** – 31,6 **II** – 57,9 **III** – 10,5	**I** – 18,2 **II** – 54,5 **III** – 27,3	**I** – 8,9 **II** – 51,1 **III** – 40,0

Note. * – r⍰0,05 it is statistically reliable in comparison with indicators of patients of group of comparison (Nyyumena-Keyls's criterion, Dunn's criterion)

he analysis of the biophysical indicators and the mineralizing potential of the oral liquid in the increased experience of endocrinopathy in the children with D of type 1 revealed the adverse dynamics of the changes. The reduction of the rate of salivation, the reduction (shift) of level pH towards acidosis, the decrease in the mineralizing potential of the oral liquid, and the subsequent increase in the frequency of the occurrence of the crystals of the III type were associated with the de-compensative character of the course of the carious process. Hippo-salivation at the late stages of the development of D of type 1 in the children, according to this research was connected with the decrease in the functional activity of the salivary glands, considering the full destruction of the insulin-producing β-cells of the pancreas and the constant presence of the excess level of glucose. Considerable reduction of the salivation in the children with an experience of D of type 1 for more than five years decreased the cleaning ability of the oral liquid, the deterioration in its buffer, the antimicrobial, re-mineralizing properties and, as a result, the reduction her caries of the protective effect. It was proven by the experts that the decrease in the salivation influences the reduction of its buffer capacity, and the prolongation of pH level in the biological film in the field of a "sour" r/n after each meal that significantly increased the risk of the development of the carious process.

The protective and adaptive homeostatic mechanisms have been the most susceptible to the changes of the acid and main balance in the oral cavity, since at the same time, the

electrochemical interactions influence the physiological properties of saliva (the degree of the mineralization and structuring, and the speed of the ion-exchange processes), and the activity of enzymes and microflorae and also the factors of humoral and fabric immunity were broken. In the children with an experience of D of type 1 for about one year in the stage of compensation mobilization, the self-adaptive reactions with the formation of the adequate adaptation changes were noted. The late stages of development of the endocrinopathy were combined with the decrease in the reserve opportunities of the organism and the involvement of the system of the specific adaptation provided an increase in the functional activity of the organism. This complex of reactions led to an overstrain of the neuro-humoral regulatory mechanisms responsible for the constancy of the internal environment and also to the pathophysiological structural changes at the cellular and fabric level.

It has been authentically established that the main role in the regulation of an oral homeostasis is played by the level of pH of the oral liquid (an indicator of activity of ions of hydrogen). At the critical value of the oral liquid's (pH =6,2) violation of its structural properties, the increase in the solubility of enamel was due to the decrease in supersaturation by Ca2 ions + and HPO42. The insignificant shift of the pH level in the alkaline party (alkalosis) maintained the oversaturation of the oral liquid with the ions of Ca2+, HPO42-, a hydroxyl ions which were a part of the apatite of the enamel prisms that promoted the improvement of the processes of the mineralization of the tooth enamel. The alkalescent level of pH of the oral liquid (7,2-7,8) was optimum (balanced) for the processes of the mineralization and remineralization of the tissues of teeth. The changes in pH level of the oral liquid towards acidosis, in the increased duration of D of type 1 in the children, was caused by the violation of the trance of the capillary and carbohydrate exchange, the high concentration of glucose in saliva, the accumulation (accumulation) of sour products, the increase in the speed of a microbic acid-producing, the increase of the acid-forming activity of the microflora of the carious cavities, and the dental raid, tension in the operation of the protective and compensatory mechanisms of the regulation of the acid and the main balance in the oral cavity, and the decrease in the overall performance of the buffer systems of saliva.

The decrease in the mineralizing properties of the oral liquid at the emergence, and the subsequent increase in the microcrystals of the III types in the complex with other diagnostic signs in the children with a long experience of D of type I was the reason of change of the oral homeostasis, the high probability of the emergence, and the de-compensative character of the course of the carious process of the dairy (constants) teeth and also the risk of the development of the inflammatory or allergic reactions in the mouth. The set of the predictive signs connected with the reduction of the mineralizing potential of the oral liquid and the increase in the number of microcrystals of the III types objectively demonstrated the decrease in the mineralizing, regulatory, protective and buffer function of saliva. The results obtained in this study have been coordinated with the published data of the domestic and foreign experts [31-33].

CONCLUSION

1. Comparing the children suffering from D type I to the healthy children, the following results were obtained: in the oral liquid which is the highly sensitive indicator of the all-somatic pathology, the statistically reliable change of the indicators of phosphorus-calcium metabolism, calcium regulating hormones, the mineralizing potential and antimicrobial protection were observed.
2. The results of the research on the parameters of phosphorus-calcium exchange indicated the markers of the bone metabolism, the biophysical and mineralizing properties of the oral liquid, in the children with the diagnosis of "D of 1 type" with an increased duration of the experience of endocrine pathology, the gained level of the general (Ca general), the ionized calcium (Ca2+), the inorganic phosphorus, a parat-hormone were noted at the decrease of the activity of alkaline phosphatase, level of the osteocaltsin, the 25th D3 hydroxy-vitamin, the speed of the salivation, the mineralizing potential and also the shift of pH level towards acidosis. The multidirectional dynamics of the changes in the adverse party in the increased duration of the endocrinopathy demonstrated the essential delay of the synthetic processes in the solid tissues of teeth, the acceleration of the processes of demineralization of enamel, the decrease in the functional activity of the salivary glands, the tension in the operation of the mechanisms of the regulation of the acid and the main balance in mouth.
3. With increase in the experience and the strengthening of the extent of the compensation of D of type I in the children changed the hygienic state to "good" – in the healthy children, to "satisfactory" – in the children with

the experience of D of type I for about one year, and to "unsatisfactory" – in the children with the endocrinopathy experience from a year to five years and from five to ten years.

4. In the early phases of the development of D of type I in the children, the compensated and sub-compensated form of the course of the carious process, the increase in the permeability of enamel, the insignificant prevalence in the solid tissues of teeth in the processes of the demineralization over the remineralization processes was revealed. The compensation of the carious process in the children with the short experience of endocrinopathy demonstrated the self-control of the mechanisms of the mineral exchange in mouth while maintaining the physiological re-mineralizing properties of the oral liquid.

5. The late phases of the development of D of type I in the children who were combined with the decompensation of the carbohydrate exchange were characterized by the high intensity and a de-compensative form of the course of the carious defeats, the low structurally functional resistance of enamel expressed by the processes of demineralization of the solid tissues of teeth. The insignificant enamel resistance and unbalance in the "demineralization-remineralization" system towards the processes of the demineralization in the children with the long experience of the endocrinopathy, caused the exhaustion of the functionality of the salivary glands, the violation of the mobilization salivary systems in response to the emergence of the cariogenic situations in mouth, changed the homeostasis on calcium, and decreased the resistance of enamel to the influence of the organic acids.

6. In the children with the long proceeding of D of type I in the oral liquid accumulation of carbohydrates, the strengthening of the exchange processes in mouth with the formation of so-called "metabolic explosion" was noted. This process which was combined with the accumulation of the sour products and the activation of anaerobic glycolysis, on one hand, promoted the strengthening of the formation of the additional structures of phosphate of calcium acting as the main mineral components of the oral liquid and the solid tissues of teeth, with another – breaking the processes of the mineralization of the teeth enamel at the expense of the imbalance of the ferment systems.

7. The level of lactoferrin in the oral liquid as a nonspecific factor of the anti-microbic protection of an oral cavity was associated both with the development of the most endocrine pathology, and the existence (character of a current) of the carious damage of teeth. The increase in the concentration of lactoferrin correlated with the moderate increase in intensity, the prevalence of the caries of teeth in the children in the early terms of the development of D of type I indicated the strengthening of the processes of the inflammation and activation of the mechanisms of the antibacterial activity. The reduction of the maintenance of lactoferrin in the oral liquid as the inflammation marker in mouth and the indicator of the character of the course of caries of teeth in the children at late stages of the development of the endocrine pathology, confirmed the critical period of decrease in the antimicrobial protection in the oral cavity, the exhaustion of the compensatory mechanisms of the oral homeostasis, the synchronization of the inflammatory processes in mouth, and the formation of the prerequisites for progressing the carious damages of teeth.

8. While progressing of D of type 1 in the children, it was established the expressed tension of the synthetic processes in the salivary glands which was shown in the decrease in the level of a secret-producing, functional activity and also the ferment-exudation functions. The reduction of the protective physiological potential of the oral liquid in the bodies of oral cavity provoked the strengthening of the inflammatory processes, the aggravation of the mechanisms of the local oxidizing stress, the formation of "the closed pathogenetic chain" of the generation (maintenance) of the cariogenic situation.

9. The level shift of pH towards to acidosis which correlated with reduction of the mineralizing potential of the oral liquid, and the increased frequency of the occurrence of the crystals of the III types were associated with the de-compensative character of the course of the carious process in the children with an experience of D of type 1 more than five years objectively proved the influence of the endocrine pathology on the saliva crystallization type. The lack of the ability of saliva to crystallization in the children in the late terms of development of D of type 1, in combination with the unsatisfactory metabolic control, proved the existence of the physiologically unstable homeostasis which was followed by the exhaustion of the reserved adaptable mechanisms of the children's organism at the endocrinopathy.

10. The widespread introduction of the modern medicine of the technologies of the noninvasive diagnostics of D of type 1 in the children demonstrated the prospects and the diagnostic importance of these research studies within the

expansion of the available, informative, safe methods directed to the decrease in risk of the infection at parenteral interventions. The extension of the list of the identification of the biological markers of the oral liquid was defined by the following indicators: the stability and accuracy of their identification, including the reproducibility and sensitivity of analyses; the simplicity of the performance of researches; the high specificity and sensitivity; the easy quantitative definition in the clinical laboratory; the economic and medico-social feasibility; and the integrity of the clinical-diagnostic algorithms.

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