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DIAGNOSIS AND SIGNIFICANCE OF GENETIC FACTORS IN CHRONIC GENERALIZED PERIODONTITIS

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Abstract:

The study is based on retrospective and prospective data obtained by monitoring patients with different severity of CTD+chronic generalized periodontitis (ChGP) pathology - 104 patients from them with DCTD (Marfan syndrome+ ChGP) -56 (group 1), with UCTD+ ChGP -48 (2nd group) people being under medical supervision in the departments of the Republican Screening Center of Uzbekistan

Keywords: Connective tissue dysplasia, chronic generalized periodontitis, mineral disorders, genetic factors

RELEVANCE. According to an analysis of WHO data from 35 countries, the prevalence of periodontal disease in persons aged 31-44 years was very high (over 75%) in 7 countries, high (40-75%) in 13 countries and moderate (less than 40%) in 15 countries [27]; also, a combination of cardiovascular pathology, rheumatism, diabetes mellitus, gastric and duodenal ulcer, temporomandibular system pathology with various periodontal pathologies was established [1, 17, 22, 25, 26]. It is known that in the embryonic period, the structure-forming function of connective tissue (CT) is manifested, which affects the differentiation and organization of tissues, including periodontal tissues [19, 20, 21, 23, 24], in addition, connective tissue dysplasia (CTD) in the embryonic and postnatal periods, due to genetically altered fibrillogenesis of the extracellular matrix, leads to homeostasis disorders at the tissue, organ and organismal levels in the form of various morphofunctional disorders of locomotor and visceral organs with a progressive course, thus, CTD is not an independent nosological entity, but a genetically determined systemic progradient process that forms phenotypic features of hereditary pathology and serves as a background for associated diseases. For example, collagen mutation - Ehlers-Danlos syndrome develops due to mutation of COL3A1, COL1A1, COL1A2 genes or Marfan syndrome - formed by mutation of the fibrillin gene, a structural protein of the connective tissue.

Periodontitis is the most common disease among all periodontal pathologies. However, specialists can confidently state that the clinical picture of aggressive forms of periodontitis with an early onset (at the age of 18-20 years) differs significantly from chronic generalized periodontitis (ChGP) in adults (older than 35 years) [24]. At the same time, some authors suggest the possibility of ChGP turning into an aggressive form in elderly patients against the background of reduced immunity [15, 17, 18, 24]. However, so far there is no consensus on this issue among specialists, in connection with which the specified problem remains relevant for research. In order to study in a comparative aspect the features of the dental status of patients with ChGD and CTD depending on gender, age and BMD, the state of hard tissues of teeth and periodontal tissues in 34 patients with moderate and severe ChGD and 104 patients with CTD was examined.

PURPOSE OF RESEARCH. To diagnose and determine the role of genetic factors in chronic generalized periodontitis with connective tissue dysplasia in order to improve the prevention and treatment of patients.

MATERIALS AND METHODS OF RESEARCH. The present study is based on retrospective and prospective data obtained from the observation of patients in 2016-2020 with different severity of CTD+chronic generalized periodontitis (ChGP) pathology - 104 patients, including 56 with DCTD (Marfan syndrome+ChGP) - (Group 1), 48 with UCTD+CjGP - (Group 2) people who were under dispensary supervision in the departments of the Republican Screening Center of Uzbekistan, as well as 34 virtually healthy individuals without signs of musculoskeletal dysplasia but with an existing diagnosis of ChGD (control group -C/G) aged 18 to 37 years who sought dental care at the clinic of the Center for the Professional Development of Medical Professionals. A total of 138 people were examined, including 72 men and 66 women, with 32 men and 24 women in Group 1 and 25 and 23 in Group 2, respectively. In terms of age groups, with Group 1, 14 patients -18-20 years; 23, 21-29 years; 19, 30-37 years; with Group 2, 14; 21; -13 patients and with C/G 12; -10; and -12 patients, respectively. The diagnosis of CTD was made on the basis of the results of a complex of general clinical investigations: questioning of a patient, general

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examination; instrumental (echopleurocardiography, computed tomography), biochemical, chemoluminescent methods. All examined patients were consulted by a geneticist to rule out chromosomal pathology, which was confirmed by karyotype studies. Also, according to the classification [13], all signs of dysplastic changes of organs and systems were divided into: locomotor, skin symptoms and visceral symptoms: In addition, microsigns of disturbed morphogenesis have been identified, such as widely spaced eye slits; anti-mongoloid incision of the eyes; arch-shaped palate; gothic palate; uneven row of teeth; central diastema; malocclusion; upper lip frenulum; and others. Also, various anthropometric methods were used to verify the phenotypic features of CTD. An important point for differential diagnosis was the collection and compilation of family genealogical anamnesis; in relatives of probands and healthy individuals were obtained by questioning, if possible, by direct examination of relatives, as well as by analyzing their medical records.

In order to assess the bone mineral density (BMD) of the tissue, computed tomography was used for this purpose, X-ray densitometry was performed in all patients; criteria were such indices as bone mineral component - the amount of mineralized tissue in bone scans; bone mineral density (BMD) in the scanned area and to assess the use of the T-criterion [2, 4, 9, 10]. In order to assess mineral metabolism and bone remodeling - bone formation and bone resorption in the C/G of 12 men and 12 women, all were examined for mineral and bone metabolism.

All patients underwent general clinical examinations: general blood and urinalysis, biochemical and laboratory diagnostics. Also, concentrations of magnesium, calcium, inorganic phosphorus, and alkaline phosphatase (ALP) activity in serum without traces of hemolysis were determined. Normal values of total calcium in blood serum in adults are 2.25-2.75 mmol/l, magnesium concentration is 0.74-1.2 mmol/l, inorganic phosphorus is 0.87-1.45 mmol/l. For calcium and phosphorus levels in urine, normal concentration values were taken to be for inorganic phosphorus -13-42 mmol/24 hours, - calcium - 2.5-7.5 mmol/24 hours. To study the hormonal profile of patients - markers of bone remodeling, homocysteine, was performed on an Immulite 2000 automatic analyzer, on the day of blood sampling [14]. The levels of triiodothyronine, thyroxine, thyrotropic hormone, cortisol, parathyroid hormone, prolactin, adrenocorticotropic and somatotropic hormone in patients without hemolysis traces were examined in serum; normal values in adults were 9.5-65 ng/ml, cortisol 138-635 nmol/l, thyroid hormone 0.4-4 mU/ml, somatotropic hormone in men 0-4 ng/ml, in women 0-18 ng/ml, adrenocorticotropic hormone <120 pg/ml, triiodothyronine 1.08-3.14 nmol/l, thyroxine 59-142 nmol/l.

The dental methods of hard tissue and periodontal assessment use parameters of various indicators, taking into account the requirements of the International Protocol for the Assessment of the Severity of Periodontal Disease (NIDCR Protocol for Periodontal Disease Assessment) [7, 8, 11, 12, 16], which includes the following indices: - Caries Index - the number of the teeth affected by caries (C), filled (F) and extracted (E), index calculation and the level of caries intensity were characterized according to the WHO recommendations: 0-1,5 - very low intensity; 1,6-6,2 - low; 6,3-12,7 - medium; 12,8-16,2 - high and more than 16,2 - very high:

- Hygiene Index (HI) (Lindhe, 1983) - which determines the presence or absence of soft plaque on all tooth surfaces. Also, the Gingival Index GI (Loe, Silness) - changes in the color of the gum and the appearance of bleeding are mandatory signs of inflammatory periodontal disease; that is; 0 - normal gum; 1 - characterizing mild gum inflammation; 2 - gum hyperemic, with a bluish tint, there is moderate swelling and - 3 - marked hyperemia and edema of the gum, tendency to spontaneous bleeding: The PBI (Papilla Bleeding Index, Saxer and Mühlemann modified by CowellL) gingival papilla bleeding index was determined and scored; the periodontal pocket depth measurement and the degree of attachment loss were studied using a button probe; diagnoses of periodontal tissue pathologies were made on the basis of BMD 10-c by K05.31.

Radiological (R) methods orthopantomography of the jaw bones was performed on an orthopantomograph. To quantify the degree of resorption of the alveolar part of the lower jaw (n/h) and the alveolar process of the upper jaw (r/h), we used the alveolar bone destruction indices - Fuchs index and R-index. MCI was used to quantitatively and qualitatively characterize the cortical layer of the n/h [4, 5, 6, 7, 13, 28]. To assess the statistical significance of the results of the study, expressed in quantitative signs, we used analysis of variance, also, to evaluate the statistical significance of the difference of group averages, using Fisher test (F-criterion) when comparing more than two groups, Student test (t-test) to compare the mean values, the results of the analysis were considered statistically significant if the error rate did not exceed 5% ($p < 0.05$).

To obtain information about genealogical data on the presence of signs of CTD in relatives of probands and healthy individuals, the method of interview was used, if possible, during direct examination of relatives, as well as during analysis of their medical records (Lisichenko O.V., Sultanova F.A., Korobkova E.H., 1975; Egorova L.V., 2000). To study the genetic component of mineral metabolism disorders in patients with XI11, the following polymorphisms were selected: calcitonin

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receptor gene CALCR, collagen al-chain gene COL 1A1, and parathyroid hormone receptor type 1 gene PTHR1. The choice of the polymorphisms under study was determined by the identified abnormalities in the calcium-regulating hormone system. One polymorphic site was investigated in each gene. They are as follows -CALCR gene; -point -c1340 C> T; -rsl801197; -T alleles; -C CT TT genotype, COLI AI gene; -point c104-4410T; -rs1800012; -GG T alleles; -G GT TTB genotype, PTHR1 gene; -point c.-48- 360G> (AAAG) 5/6/7; rsl0533296; alleles 5 67; genotype 55 56 6 7 66 67 77 57 with designation. Both individual polymorphisms and their possible combined effect were studied in 104 patients participating in the study (57 men, including 32 in group 1, 25 in group 2 and 47 women, 24 in group 1, 23 in group 2) and 24 people in the C/G (with their consent). Based on the data obtained, we calculated the frequencies of genotypes in groups 1and 2 of patients in whom mineral metabolism disorders were detected.

RESULTS AND DISCUSSION. As can be seen from the results obtained on the dental status in the studied groups; in the 1st group of patients with Marfan syndrome, caries intensity averaged -18.2±0.5; the ratio of KPU elements, - C -2.1±0.5; F-16.8±0.4; E -2.8±0.3 out of 24.7±0.4 total teeth; while non-carious dental lesions made -9.0±0.4; parodontal tissue pathology -90.6±0.6. Among Group 2 patients with DCTD pathologies, these indices were -16.7±0.8; -2.1±0.4; -13.3±0.4; -3.2±0.4; -26.1±0.4; -4.5±0.3; -85.5±0.8, respectively. If we compare the incidence of pathology by age in the 1st group, we will note that at the age of 18-20 the carious pathologies were -16,4±0,6; -1,1±0,3; -15,1±0,8; -1,4±0,2; -26.6±0.2 respectively, non-carious lesions -4.8±0.6 and periodontal pathology -85.7±1.7, then already at the age of 30-37 these indicators were -19.6±0.4; -3.1±0.6; -18.1±0.2; -4.4±0.4; -22.6±0.8; -13.4±0.8; -94.7±1.2 respectively. As can be seen, the intensity of all these pathologies - carious and non-carious dental hard tissue lesions and periodontal disease increases in direct correlation with the age of patients. The same trend is observed in Group 2 patients, while a different picture is observed in the CG subjects - i.e., those who are absolutely healthy on the CT side. Intensity of carious and non-carious dental lesions and periodontal pathology in CG patients was lower than in patients of groups 1 and 2. At the same time, the number of affected teeth with caries and extracted teeth complicated by caries and periodontal pathology was higher in group 1 than in group 2.

A comparative assessment of periodontal tissues between the sexes showed a statistically significant difference in all the studied indicators, with women having more severe forms of tissue inflammation. The results shown in Table 3, hygienic and clinical condition of the oral cavity of patients of groups 1 and 2 correspond to the literature data [1, 25, 28]. Analyzing oral hygiene conditions in patients diagnosed with Marfan syndrome - the following indicators are noted: hygiene index -22.5±1.9; bleeding index -2.7±0.3; gingival index -2.5±0.3; periodontal pocket depth -6.9±0.5; attachment loss value -8.1±0.5; tooth mobility -2.5±0.8 with the diagnosis of DCTD these indicators are -31.9±1.5; -1.9±0.3; -1.9±0.5; -4.5±0.7; -5.6±0.4; -1.6±0.6 respectively; in the CG -66.1±1.6; -0.5±0.2; -0.5±0.1; -0.7±0.1; -1.1±0.1; no mobility of teeth. Also in groups 1 and 2 of patients there is a deterioration of these indicators, oral hygiene is directly related to age indicators. The periodontal pocket depth in patients with Marfan syndrome aged 18-20 years -5.4±0.1; 21-29 years -6.4±0.4; 30-37 years -8.8±0.6 in patients with DCTD pathology -3.2±0.1; -4.4±0.8; -5.8±0.8 respectively. According to the results of the data obtained, we can conclude that in patients with CTD there are more frequent lesions of oral organs and tissues; more frequent caries and more significant destruction of periodontal tissues, accompanied by severe bleeding and hyperemia of gingival tissues.

According to the results of bone mineral density study; R-index and determination of Fuchs bone number; - Fuchs index in group 1 patients averaged 0.48±0.03, which corresponds to the degree of bone resorption of the alveolar part within 1/2 to 2/3 of the root length. The R-index bone loss was 1.54±0.08, which is 68% of the loss from the total height of the alveolar process. Bone resorption of the alveolar process in patients of the 1st group was 1.88±0.18 (72%), which was greater than 1.72±0.08 for the n/h (65%) (p>0,2). The value of the Fuchs index, which determines the level of resorption, was on average almost the same (p>0.5) in both jaws. In order to study the peculiarities of bone resorption of the alveolar part of the jaws, in patients with different age groups, a comparative assessment of bone tissue condition was performed, with a high sensitivity of bone tissue to various external and internal influences being noted, e.g., decreased functional load due to inflammatory periodontal disease or impaired hormonal regulation of mineral metabolism concerning especially Group 1 and Group 2 patients. The spongy bone is subject to such changes to a greater extent, which is marked by a shift of the remodeling process toward an increase in osteoclastic resorption, in contrast to cortical bone tissue, in which the rate of metabolic processes is 6-7 times lower than in CG. At the same time, the degree of alveolar bone loss in the c/h was almost independent of the age of patients in the CG, in contrast to the n/h, at 30-37 years, the level of alveolar resorption was 0.22±0.02 (up to 1/4 root length), which is almost 4 times lower than the Fuchs index in the 1st and 2nd

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groups up to 35 years 0.80±0.04 (up to 1/2 root length) (p <0,005). Hence, we can conclude that with age, bone loss in the alveolar part of the m/hr in all patients with CTD occurs faster than in the alveolar process of the m/hr. R-analysis of all groups confirms that the level of resorption of osteotropic hormones in patients with early-onset ChHD, the effect of which enhances bone loss and reduces its MF.

The high correlation between the BMD of the skeletal tissue and the MCI n/h index in different somatic pathologies, proved by many studies, makes it possible to use it as a stomatological criterion for assessing the decrease in the BMD of the axial skeleton. Based on our results of alveolar bone resorption values in the v/h and n/h of patients 30-37 years old, we can see that bone loss in the alveolar process area in the upper jaw occurs somewhat faster (68%) than in the lower jaw (48%) (p <0,3). Thus, it should be noted that the degree and magnitude of alveolar bone resorption of both jaws in patients with CTD pathologies increases with age and early onset of the disease, alveolar bone resorption, is more often noted in the area of the maxilla.

We know that stimuli initiate the process of bone formation and bone resorption, but this data is still a subject of scientific debate. Currently, the most developed concept is the stimulating and regulating effect of a number of osteotropic hormones on osteosynthesis. The main ones are: parathyroid hormone, calcitonin, vitamin B hormone, thyroid, gender hormones and growth hormone. For comparison, the basic quantitative indicators of mineral metabolism and regulatory hormones in practically healthy men and women, as we pointed out, were examined in 24 practically healthy people; the results showed that calcium content was -2.50±0.41 mmol/l; phosphorus -1.42±0.22 mmol/l and magnesium -0.97±0.06 in blood and phosphorus in urine -37.2±2.35 mol/l daily for 20-37 year-old practically healthy people: Hormonal parameters - somatotropic hormone -4.4±0.24 mg/ml; ACTH -16.46±1.6 pg/ml; cortisol -530±39 nmol/ml; thyroid hormone -1.29±0.2 mU/ml; triiodothyronine -1.88±0.1 nmol/L; thyroxine -85.25±4.68 nmol/mL; prolactin -222±14 mU/mL; parathyroid hormone -37.68±3.76 pg/mL: Biochemical markers of metabolism: alkaline phosphatase-68.08±4.6ed/l; osteocalcin-13.56±1.8ng/ml; urinary deoxypyridinoline-6.2±0.31mol/creatinine/day; urinary calcium-4.44±0.4 mmol/day; plasma homocysteine-13.88±0.08 μmol/l.

The results of the study of individual features of tissue BMD and bone metabolism state in patients with ChGD, DCTD+ChGD and UCTD+ChGD in a comparative aspect, the presence of correlation links between decreased BMD and dental pathology greatly facilitates the search for diagnostic criteria for these pathologies. The influence of various somatic diseases on the development and course of dental pathology has long been recognized, and their role in the pathogenesis of various periodontopathies has been studied in sufficient detail. However, until now, there are no clear dental criteria, the presence of which in the mouth would allow a diagnosis of decreased BMD. The objectives of our study also included the determination of diagnostic criteria for decreased BMD and mineral metabolism according to the dental status of patients with ChHD and OP. These relationships are manifold and different in nature, in order to reveal them an intra-group correlation analysis was performed, which allowed us to identify similar correlations in different groups of patients, CG, Group 1 and Group 2, and to highlight some specific features. Correlation matrices were built for correlation analysis, from which statistically significant results were selected with reliability p<0.05 and relationships were determined by Pearson coefficient value. The indexes of KPU and periodontal indexes characterizing the condition of hard tissues of teeth and periodontium were considered as outcome indicators. The analysis revealed the following significant correlations: especially in group 1, there was a high level of correlation between the number of extracted teeth and BMD (r=-0.412 at p=0.011). Considering the inverse nature of the obtained pattern, we can state that a decrease in BMD in group 1 patients with DCTD+ChGP leads to an increase in the number of extracted teeth. This is most likely due to periodontal problems, since the intensity of the carious process in Group 1 women was at an average level (the average C+F value in the group was 18.4±1.8). Consequently, a decrease in BMD can be an aggravating factor in the course of periodontal pathology in group 2 - UCTD+ChGP. The degree of tooth mobility determined the severity of inflammation symptoms (RV1) (r=0.456 at p=0.013) and depended on the depth of periodontal pocket (r=0.621 at p=0.0008). This conclusion is quite consistent with clinical observations. When assessing the impact of mineral metabolism parameters on the condition of hard dental tissues in CG patients, no significant correlations were noted. Also, interesting results were obtained when studying the correlation relationships in young and middle-aged men of groups 1 and 2.

The genetic nature of the majority of common chronic diseases, including ChGD_DCTD and ChGD+UDCTD, continues to be one of the most challenging problems of medical genetics. In our opinion, the etiopathogenesis of this form of periodontal pathology is a complex interrelated chain of various systemic and local factors, not the least of which is hereditary predisposition. Perhaps it is genetics that can play a decisive role in understanding the mechanisms of development, treatment, and prevention of this

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common pathology. Based on the clinical picture of the course of ChGD in DCTD and UDCTD and the data of laboratory tests determining the state of mineral metabolism, the calcitonin receptor gene (CALCR), the a 1-chain collagen gene (COLIA1) and the parathyroid hormone receptor type 1 gene were selected for the study of polymorphisms (*PTHR1*). *Based on a study of the calcitonin receptor gene {CALCR) [460], two restriction fragment length polymorphisms detected by restrictases AluI and TaqI were found, which showed that holders of the 7T genotype have on average lower BMD values compared with those of the CC genotype*. In our study, we also examined the frequency of CAbs genotypes among ChGP patients compared with CTD pathologies (DCTD and UDCTD)

Table №1

Distribution of allele and genotype frequencies of the calcitonin receptor gene (CABSC) in patients with Marfan syndrome+ChGD and UDCTD+ChGD.

Genotype	Group 1 (Marfan syndrome)		Group 2 (UCTD)	
	N (P=56)	**%**	N (P=48)	**%**
CC	10	12,26	8	8,4
CT	18	24,32	19	42,34
TT	28	68,42	21	54,8
X^2=4,021 (p>0,05)				
Alleles	N	**%**	N	**%**
C	14	25,0	29,5	24,85
T	42	75,0	106,5	75,25
%~=0,164 (p>0,5)				

The incidence of CC- and 7T-genotype associated with decreased BMD was slightly higher in the first group (12.86% and 68.462%, respectively) than in the second (8.4% and 54.90%), but there was no statistically significant difference in this index (p>0,05). At the same time, homozygotes for the T allele were in the absolute majority in both groups 1 and 2, compared to heterozygotes (ST -24.42% in group 1 and 38.50% in group 2) and homozygotes for the C allele (14.38% in group 1 and 6.8% in group 2). The same patterns were found when analyzing allele frequencies. The C allele was in the minority in both groups, while the G allele was dominant in both groups.

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Table №2
Condition of hard tissues of teeth and periodontium in patients with CTD + ChGD and ChGD of severe degree depending on the polymorphism of calcitonin receptor gene (CABC)

	CC	***CT***	***TT***	p-value of Fisher's criterion
	1-я груп. N=56	2-я груп. N=48	К/Г. N=24	
Number of carious teeth	2,1±0,5	2,1±0,4	1,2±0,8	p>0,05
Number of filled teeth	16,8±0,4	13,3±0,4	8,4 ±0,2	<table><tr><td></td><td>cc</td><td>CT</td><td>TT</td></tr><tr><td>CC</td><td>-</td><td>0,038</td><td>0,597</td></tr><tr><td>CT</td><td></td><td>-</td><td>0,021</td></tr><tr><td>TT</td><td></td><td></td><td>-</td></tr></table>
Number of carious and filled teeth	18,9±1,1	15,4±0,8	9,6±1,1	<table><tr><td></td><td>cc</td><td>CT</td><td>TT</td></tr><tr><td>cc</td><td>-</td><td>0,027</td><td>0,469</td></tr><tr><td>CT</td><td></td><td>-</td><td>0,023</td></tr><tr><td>TT</td><td></td><td></td><td>-</td></tr></table>
Number of extracted teeth	2,8±0,3	3,2±0,4	6,1± 0,1	p>0,05
Total teeth	24,7±0,4	25,0±1,4	24,8±0,2	p>0,05
Hygiene index H1	22,5±1,9	31,9±1,5	66,1±1,6	p>0,05
RV1 index	2,7±0,3	1,9±0,3	0,5±0,2	p>0,05
Index C1	2,5±0,3	1,9±0,5	0,5±0,1	p>0,05
Periodontal pocket depth (mm)	6,9±0,5	4,5±0,7	7±0,1	p>0,05
Tooth mobility	2,5±0,8	1,6±0,6	-	p>0,05

At the same time, statistically significant differences were obtained in the BMD score, also recorded at different polymorphisms, which were within the normal range.

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Currently, there are numerous publications confirming the association of the Spl polymorphism of the COLI AI gene with the development of ChGP. However, we could not find any studies on the association of allelic frequencies or allelic variants of the COLI AI gene with Marfan syndrome+ChHD and UDCTD+ChHD. Given the important role that collagen plays in bone tissue formation, as well as based on the data obtained by studying the level of bone formation marker (serum osteocalcin), it is reasonable to assume that mutations in this gene may also influence the development of ChGD accompanied by active lysis of alveolar bone in CTD. The frequency of TT genotypes associated with decreased BMD in patients with Marfan syndrome+ChGP and UDCTD+CGP was significantly higher (48.85%) than in the K/G (12.50%) ($p<0.001$). Homozygotes for the GG allele associated with normal BMD were significantly less common (29.47%) among patients in groups 1 and 2 than in K/G (68.46%) ($p<0.001$).

The role that paraschyte hormone (PTH) plays in the regulation of calcium homeostasis and mineral metabolism is well known. High levels of PTH inhibit the metabolic activity of osteoblasts, decrease the protein levels of collagen type 1, and modulate the levels of various osteoblast markers, including osteocalcin. The signaling effect of PTH on osteoblasts is carried out through the activation of specific parathyroid hormone type 1 receptors, which belong to the 2nd class of receptors of the secretin family, conjugated to the G-protein. Type 1 parathyroid hormone receptor gene mapped and sequenced. Given the clinical and laboratory data obtained in our work, we also included in the study the influence of the polymorphism of the parathyroid hormone receptor type 1 gene (PTHRI) on the development of ChGD with an aggressive course. The amino acid repeat frequency encoded as 5\5 is considered normal; those with a repeat frequency of 5\6, 6\6, or 7\6 in the genotype have a parathyroid hormone receptor type 1 gene abnormality.

The frequency of PTHRI genotype allelic variants defined as pathology (heterozygotes 5/6 and homozygotes 6/6) in group 1 (AFP) was 51.7%; homozygotes for allele 5 were 59.5%.

Table №3

Distribution of allele frequencies and genotypes of the parathyroid hormone receptor type 1 gene (PTHR) in Marfan syndrome+ChHD and UDCTD+ChHD**.**

Genotype	Group 1 (Marfan syndrome)		Group 2 (UCTD)	
	N (P=56)	**%**	N (P=48)	**%**
5/5	29	51,78	28	58,3
5/6	16	28,57	20	41,7
6/5	11	19,64	-	-
X^2=4,021 (p>0,05)				
Alleles	N	**%**	N	**%**
5	59,8	65,8	114,8	68,8
6	14,5	15,8	16,7	14,9
¿3,607 (p=0,208))				

The multifactorial model is based on a simple ideology: if the group of genes under study is related to the development of a chronic disease, then their certain alleles, which are called predisposing alleles, should occur more frequently in patients than in the population. Other alleles of the same genes should occur less frequently and play a protective role. In this case, the search for candidate genes should be carried out based on ideas about the pathogenesis of the disease under study. Based on the results of our own study, we hypothesized the presence in the pathogenesis of aggressive forms of ChGD in CTD associated with an imbalance of calcium-regulating hormones. Therefore, a group of genes determining such disorders was taken as the basis for the genetic component of the multifactorial model of periodontitis. After combining the three polymorphisms, 29 genotype combinations were obtained. Absolute normal (SSUS\55) among patients in groups 1 and 2, was detected in 4.8% of cases (5 people). Based on the results of our own study, patients' anamnestic data, and the theory that genes influence susceptibility to diseases of common origin, our work suggests the need to search for markers among diseases accompanied by CTD. We studied both individual polymorphisms of the calcitonin receptor gene (CALCR), collagen a1-chain

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gene (COLIA), and parathyroid hormone receptor type 1 gene (PTHR) and their possible combined effect, since it is known that diseases, in the etiology of which a genetic component is essential, but the character of inheritance cannot be explained by simple Mendelian rules, and the phenotype is determined by the influence of environmental factors, form a group of so-called multifactorial diseases.

CONCLUSION.

Thus, the state of dental hard tissues on the background of reduced bone mineral density is characterized by a high intensity of the carious process and a significant number of extracted teeth. The high correlation between the state of calcium homeostasis and the intensity of the carious process indicates the cause of secondary adentia in patients with reduced skeletal BMD - mineralization disorders of dental hard tissues. Also, patients with CTD have changes in the periodontal tissues characteristic of severe periodontal pathology. At the same time, the course of severe ChGD in young and middle-aged individuals has gender differences. In addition, the high intensity of the carious process in young and middle-aged patients without inflammatory periodontal pathology, especially in patients with Marfan syndrome, can serve as a diagnostic criterion of decreased BMD.

Low BMD may be related to the level of alveolar bone resorption; loss of alveolar bone in ChGD is more pronounced, in Marfan syndrome + ChGD and UDCTD + ChGD, alveolar bone loss is generalized, uniform in the area of all teeth, with preservation of the interalveolar septum shape and cortical plate continuity, and a clear pattern of bone bars is seen on the orthopantomogram of the jaws against the background of the general porosity of the bone tissue.

An imbalance in the calcium-regulating hormone system in middle-aged patients with DCTD and UDCTD of both sexes contributes to the aggressive course of the disease, which is determined by a significantly significant ($p<0.05$) deterioration of all periodontal indexes, an increase in attachment loss and a greater degree of bone tissue resorption. The mechanism of alveolar bone resorption in middle-aged patients with CTD pathology is based on the disruption of the bone remodeling cycle on the background of calcium-regulating hormone imbalance. Decreased rate of bone formation on the background of a normal level of bone resorption is the cause of dental and periodontal tissue pathology.

Polymorphisms of some genes determining BMD (calcitonin receptor gene (CALCR), al-chain collagen type I gene (<COLLAI) and parathyroid hormone receptor type 1 gene play a role in predisposition to ChGD development *(PTHRJ)).* A significant representation of the rare T allele of the al-cepy collagen type I gene was detected among patients with Marfan+ChGD syndrome and UDCTD+ChGD with an aggressive course (*COLIA1*). The combination of homozygotes for rare alleles of these genotypes may be part of the genetic component of a multifactorial model of generalized periodontitis.

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