Diagnosis And Clinical Course of Chronic Generalised Periodontitis in Connective Tissue Dysplasia

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ABSTRACT

The present study focuses on 104 patients with differentiated connective tissue dysplasia (DCTD) (Marfan syndrome) and undifferentiated connective tissue dysplasia (UDCTD). General clinical investigations - questioning, physical examination, instrumental, biochemical, and chemoluminescent procedures were used.

Keywords: Connective Tissue Dysplasia, Chronic Generalized Periodontitis, Mineral Disorders, Marfan Syndrome.

Relevance. The prevalence of periodontal disease is known to be higher than 75% (very high) in 7 countries for persons aged 31-44 years, 40-75% (high) in 13 countries and less than 40% (moderate) in 15 countries, according to WHO data analysis [23]. Today, identifying periodontal pathology is not very difficult, especially in the advanced stages of the disease. At the same time, determining the nature of the clinical course, differential diagnosis of the nosological forms, the prognosis of the disease, its relationship with the general condition of the patient and with changes in the dental-alveolar complex and the bone system as a whole is a more complex task that requires further careful study [3, 8,16]. Also, a combination of cardiovascular pathology, rheumatism, diabetes mellitus, high gastroduodenal system pathology, gastric and duodenal ulcers and various periodontal pathologies were found [1, 5,8, 22,25]. The authors argue that bone is an active metabolic system that is constantly self-renewing through processes of resorption and formation. Bone, however, is not only a supporting organ, but also the most important participant in mineral metabolism with a significant reserve of inorganic phase. Systemic factors - such as parathyroid hormone (PTH), calcitonins (CT), calcitriols, glucocorticoids, gender hormones - are directly involved in calcium homeostasis; local factors - like cytokines and prostaglandins - make up the complex mechanism of development of chronic periodontitis (ChP), these processes remain the most interesting, important but unresolved issue amongst medical researchers at present.

We know that during the embryonic period, the structure-forming function of connective tissue (CT) is evident, which affects the differentiation and organization of tissues, including periodontal tissues [10,13, 18, 19, 25,]. Connective tissue dysplasia (CTD) processes in the embryonic and postnatal periods, due to genetically altered fibrillogenesis of the extracellular matrix, leading to homeostasis disorder at the tissue, organ and organismal levels in the form of various morphofunctional disorders of locomotor and visceral organs with a progressive course.It is also known that CTD is not a nosological entity, but that it is a genetically determined systemic progradient process that forms the phenotypic features of hereditary pathology and serves as a background for associated diseases, such as collagen mutations that lead to various diseases, including Ehlers-Danlos syndrome due to mutations in the COL3A1 (at least 30), COL1A1, COL1A2 genes, or in Marfan syndrome due to mutations in the fibrillin gene, a SP structural protein [1, 18, 24,25,26]. Thus, it can be surmised from the analysis of the literature that underlying diseases associated with genetically determined disorders of the CT is a molecular cellular pathology that leads to changes in the structure and function of all types of CT, while studying these components of the complex mechanism for the development of chronic periodontitis (ChP) remains the most interesting and important problem at the present time.

Research objective. To diagnose and study the features of the clinical course of chronic generalized periodontitis (ChGP) in patients with connective tissue dysplasia (CTD).

Materials and methods of the study. The present study is based on retrospective data from the follow-up of patients in 2016-2020 with varying degrees of CTD who were under dispensary care in the departments of the Republican Screening Centre of Uzbekistan. We examined and studied some data from the medical records of patients with hereditary CTD, with differentiated connective tissue dysplasia (DCTD) (Marfan syndrome) -56 people, including -32 (57.1%) men, -24 (42.8%) women and with undifferentiated connective tissue dysplasia (UDCTD) -48 people, including -25 (52.1%) men, -23 (47.9%) women; and -34 practically healthy persons, including -15 (44,1%) men and -19 (55,9%) women without symptoms of bone and muscular dysplasia, total -137 patients at the age of 18 to 37 years; of them 18-20 years old -40 (29%); 21-29 years old -54 (39,1%) and 30-37 years old -44 (31,2%) patients applied to the clinic of "Stomatology, pediatric dentistry and orthodontics" department of Professional Development Centre for Medical Staff.

The results were obtained by studying retrospective data and analysis of medical charts of patients with CTD pathologies, who were diagnosed with DCTD and UDCTD on the basis of general clinical examination - questioning, general examination, instrumental, biochemical, chemoluminescence methods. All those examined were consulted by a geneticist to rule out chromosomal abnormalities, which was confirmed by karyotype examination. Also, according to the classification proposed by the authors [15], all signs of dysplastic-dependent changes in organs and systems have been divided into: locomotor, skin symptoms, visceral: In addition, micro features of impaired morphogenesis have been identified; anti-mongoloid incision of the eyes; arch-shaped palate; gothic palate; irregular teeth; central diastema; malocclusion; upper lip frenulum and others. An important point for the differential diagnosis was the collection and compilation of family genealogical history. Various anthropometric methods were used to verify the phenotypic features of CTD.Also, information on the presence of signs of CTD in relatives of probands and healthy individuals was obtained by questioning, if possible, by direct examination of the relatives and by reviewing their medical records. A genealogical study established the hereditary nature of the disease [11].In accordance with the aim and objectives of the work, all patients with hereditary CTD and the control group (CG) underwent the following outpatient paraclinical examinations: quantitative bone computed tomography, electrocardiography,

echodopleurocardiography, biochemical and chemiluminescence studies.

For the purpose of examining bone mineral density (BMD), several methods were carried out, the criteria being bone mineral content and bone mineral density in the scanned area and for assessment using the T-criterion [5]; Also, in order to assess and compare mineral metabolism and bone remodelling in 24 healthy people (CG), 12 males and 12 females were studied. Also, general clinical examinations - blood and urine tests, biochemical methods of laboratory diagnostics were carried out using devices produced in the Czech Republic.Magnesium, total calcium, inorganic phosphorus and alkaline phosphatase (AP) activity were determined on this analyser in serum without traces of haemolysis.Normal values for serum calcium were -2.25-2.75 mmol/l; magnesium -0.74-1.2 mmol/l; inorganic phosphorus -0.87-1.45 mmol/l [4].For calcium and phosphorus levels in urine, normal values for inorganic phosphorus concentrations were -13-42 mmol/24 hours; for calcium -2.5-7.5 mmol/24 hours with an average calcium intake.Also, with the help of the -Immulite-2000 autanalyser, hormonal profile - markers of bone remodelling in the blood were studied [7]. Triiodothyronine, thyroxine, thyrotropic hormone, cortisol, parathyroid hormone, prolactin, adrenocorticotropic and somatotropic hormone levels were determined in serum obtained from the elbow vein. Normal levels of parathyroid hormone are -9.5-65 ng/ml, cortisol -138-635 nmol/l, thyrotropic hormone -0.4-4 mU/ml, somatotropic hormone in males-0-4 ng/ml, in females -0-18 ng/ml, adrenocorticotropic hormone <120pg/ml, triiodothyronine-1.08-3.14 nmol/l and thyroxine-59-142 nmol/l.

Dental assessment of periodontal tissues and diagnosis of periodontal tissue pathology was based on BMD 10-C (grades - K05.31) and assessment of periodontal disease severity [4,5,8,20], including the following indices; - CPU index - number of teeth affected by caries (C), filled (F) and extracted (E), index calculation and level of caries intensity were characterised according to WHO recommendations; -HygieneIndex (HI) according to theLindhe method, 1983; -Gingival index -GI [23]; -PBI (Papilla Bleeding Index); -Measurement of periodontal pocket depth and degree of attachment loss.

Radiological (R) methods to assess the condition of the jaw bone - conducted on an orthopantomograph; to quantify the degree of resorption of the alveolar part of the mandible (n/h) and the alveolar process (a/o) of the upper jaw (c/h), alveolar bone destruction indices - Fuchs index and R-index were used. For quantitative and qualitative characteristics of the cortical layer of the n/h, the MCI index according to Klemetti.E [21]; - computed tomography (CT) was used to assess the bone mineral density (BMD) of the trabecular and cortical bone tissue; all patients underwent R of the lumbar spine at L\ - L4 and the proximal femurs on the right and left and comparison of the MCT with the normal T and Z criteria.

Results and discussion. To compare the main quantitative indices of mineral metabolism and regulatory hormones in practically healthy men and women aged 20-37 years, 24 practical healthy men and women were examined; among them, calcium -2.50±0.41 mmol/l; phosphorus -1.42±0.22 mmol/l and magnesium -0.97±0.06 in blood and phosphorus -37.2±2.35 mol/l in urine. Hormonal parameters, somatotropic hormone -4.4±0.24mg/ml; ACTH -16.46±1.6pg/ml; cortisol -530±39nmol/ml; thyroid hormone -1.29±0.2mE/ml; triiodothyronine -1.88±0.1nmol/l; thyroxine -85.25±4.68nmol/mL; prolactin -222±14mmE/mL; parathyroid hormone -37.68±3.76pg/mL.Biochemical markers: AP -68.08±4.6d/l, osteocalcin -13.56±1.8ng/ml, urinary deoxypyridinoline -6.2±0.31mol/creatinine/day; urinary calcium -4.44±0.4mmol/day; plasma homocysteine -13.88±0.08mcmol/l.

According to the results obtained in the 1st group - patients with Marfan syndrome, the figures were: caries intensity - 18,2±0,5 on the average; ratio of KPU, K -2,1±0,5; P -16,8±0,4; U -2,8±0,3 from total 24,7±0,4 teeth; at that non-carious dental lesions -9,0±0,4; periodontal tissue pathology - 90,6±0,6. Among patients of

the 2nd group - with pathology of DCTD, caries intensity on the average -16,7±0,8; correlation of KPU elements; -2,1±0,4; F -13,3±0,4; E -3,2±0,4 from total -26,1±0,4 teeth; thus non-carious lesions of teeth -4,5±0,3; periodontal tissue pathology -85,5±0,8.According to the results of indicators of caries, non-carious dental lesions and periodontal tissue affection of groups 1 and 2, it can be noted that in all age groups 1 group patients have more caries, non-carious lesions and periodontal tissue affection than group 2 patients; at the same time in CG patients caries, non-carious lesions and periodontal tissue affection occur in 20% to 2 times less than group 1 and group 2 patients. Analysis of the results confirms that all types of dental pathology: carious and non-carious dental hard tissue lesions and periodontal disease increase in direct correlation with the age of patients in each group, also these indicators for CG patients were lower than in groups 1 and 2.

A comparative assessment of periodontal tissue status between the genders showed a statistically significant difference in all studied indicators. In women, more severe inflammation of periodontal tissues was observed, consistent with some of the literature, as they believe that bone demineralisation in women is associated with loss of reproductive function, overall, the authors found that the incidence of periodontal disease, with different functional status of the reproductive glands [14] in women aged 15 to 30 years is -26.6%, after 30 years the incidence of periodontal disease increases to -58.7%, and after 45 years and menopause increases to -66.6%, also found that periodontal pathology in women with poor ovarian function increases to -25%. In addition, the general condition of patients with CTD makes brushing teeth difficult, to the point of being almost impossible, due to severe clinical symptoms such as - pain in the mouth, especially the periodontal tissues.

The results of the assessment of the periodontal tissues of the patients are presented in table 1

Table 1.

Assessment of oral hygiene and periodontal tissue status of the patients examined (M±nв %-x).

M+nin %	Ageandnumber	Periodontaldiseases	Hygieneindex (H1)	Bleedingindex (BI)	Gingival index	Periodontalpocketdepth (mm)	Magnitude of attachment loss (mm)	Tooth mobility
Marfan syndrome - 56/40.6 (group 1)	18-20 years old– 14	85,7±1,7	28,5±1,7	2,1 ±0,1	1,8±0,4	5,4±0,1	6,1 ±0,1	1,7±0,1
	21-29 years old– 23	91,3±1,2	22,5±1,8	2,9 ±0,2	2,8±0,4	6,4±0,4	8,1 ±0,7	2,7±0,8
	30-37 years old- 19	94,7±1,2	16,4±2,1	3,0 ±0,1	3,0±0,2	8,8±0,6	10,0 ±0,8	3,0±0,4
	Average - 18-37 yearsold	90,6±0,6	22,5±1,9	2,7 ±0,3	2,5±0,3	6,9±0,5	8,1 ±0,5	2,5±0,8
UDCTD - 48/34.8 (group 2)	18-20 yearsold- 14	78,6±1,4	34,8±1,6	1,4 ±0,1	1,4±0,2	3,2±0,1	5,1 ±0,2	1,1±0,1
	21-29 yearsold– 21	85,7±1,6	32,6±1,4	1,9 ±0,4	2,0±0,6	4,4±0,8	5,3 ±0,4	1,6±0,4
	30-37 yearsold- 13	92,3±1,6	28,2±1,6	2,4 ±0,6	2,2±0,4	5,8±0,8	6,4 ±0,5	2,2±0,2
	Average - 18-37 yearsold	85,5±0,8	31,9±1,5	1,9 ±0,3	1,9±0,5	4,5±0,7	5,6 ±0,4	1,6±0,6
Controlgroup - 34/24.6 (CG)	18-20 yearsold – 12	58,3±1,8	62,3±1,6	0,5±0,1	0,3±0,1	0,5±0,1	0,8±0,1	-
	21-29 yearsold - 10	60,0±1,4	67,8±1,4	0,6±0,1	0,8±0,1	0,9±0,1	1,1±0,1	-
	30-37 yearsold - 12	58,3±0,8	68,3±2,1	0,4±0,1	0,3±0,1	0,8±0,1	1,1±0,1	-
	Average- 18-37 yearsold	58,8±0,6	66,1±1,6	0,5±0,2	0,5±0,1	0,7±0,1	1,1±0,1	-
Totalbyagegroup - 138/100	18-20 yearsold – 40	74,2±1,2	41,8±1,8	1,3±0,2	1,2±0,2	3,1±0,8	4,0±0,8	0,9±0,8
	21-29 yearsold– 54	79,0±1,4	40,9±2,1	1,8±0,1	2,2±0,4	3,9±0,7	4,8±0,6	1,4±0,8
	30-37 yearsold - 44	81,8±0,8	38,9±1,6	1,9±0,3	1,8±0,1	4,1±0,4	5,8±0,9	1,7±0,6
Average	138 people	78,3±1,2	40,5±1,4	1,7±0,3	1,7±0,3	3,7±0,6	4,9±0,7	1,3±0,6

Analysing oral hygiene status of patients diagnosed with Marfan syndrome, the average indices are: periodontal disease -91%; hygiene index - 22.5±1.9; bleeding index -2.7±0.3; gingival index -2.5±0.3; periodontal pocket depth -6.9±0.5u; attachment loss value -8.1±0.5; tooth mobility -2.5±0.8; with the diagnosis of UDCTD these indicators; -85.5%; -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 cohort -58.5%; -66.1±1.6; -0.5±0.2; -0.5±0.1; -0.7±0.1; -1.1±0.1; no dental mobility. Also, Group 1 and 2 patients show a worsening of oral hygiene indicators in direct correlation with increasing age. 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 or in patients with UDCTD pathology 3.2±0.1; -4.4±0.8; -5.8±0.8 respectively. Thus, the results confirm that patients with CTD have a high level of oral organ and tissue damage, such as to the teeth and periodontal tissues; destructive periodontal tissue processes, marked bleeding and hyperemia of the gingival tissues.

According to the CG scan, the total value of the Fuchs index in the 1st group averaged -0.48±0.03, corresponding to a degree of bone resorption of the alveolar part ranging from 1/2 to 2/3 of the root length, while the R-index bone loss was -1.54±0.08, which was 68% of the total alveolar bone loss. The bone resorption of the alveolar process in the first group was -1.88±0.18 (72%), higher than in the second group (-1.72±0.08 (65%) ($p>0.2$); the Fuchs index was almost the same ($p>0.5$) in both jaws. When analysing the results of bone resorption studies of the alveolar part of the jaw, the bone tissue is highly sensitive to various external and internal influences, such as decreased functional load caused by inflammatory periodontal disease or impaired hormonal regulation of mineral metabolism, especially in group 1 and 2 patients. To a greater extent, cancellous bone undergoes these changes, which are marked by a shift in the remodelling process towards increased osteoclastic resorption, in contrast to cortical bone tissue in which the rate of metabolic processes is 6-7 times lower than in CG.

The degree of alveolar bone loss in the c/h period was practically independent of the patients' age in the CG group, in

contrast to the n/h period, where the resorption rate of the alveolar part was -0.22±0.02 (up to 1/4 of the root length) at 30-37 years of age, which is almost 4 times lower than in the 1st and 2nd groups (up to 35 years) - -0.80±0.04 (up to 1/2 root length) ($p<0.005$). It can be deduced that with age and bone loss in the alveolar portion of the m/h in all patients with CTD occurs more rapidly than in the alveolar process of the m/h. Also, R-analysis in all groups confirms that resorption levels of osteotropic hormones in patients with early-onset generalised periodontitis exacerbate bone loss and reduce bone mass. The results obtained by us and by some researchers prove a high correlation between the BMD of the skeletal tissue and the MCI n/h index, in different somatic pathologies, which makes it possible to use it as a dental criterion for reducing the BMD of the axial skeleton [2].

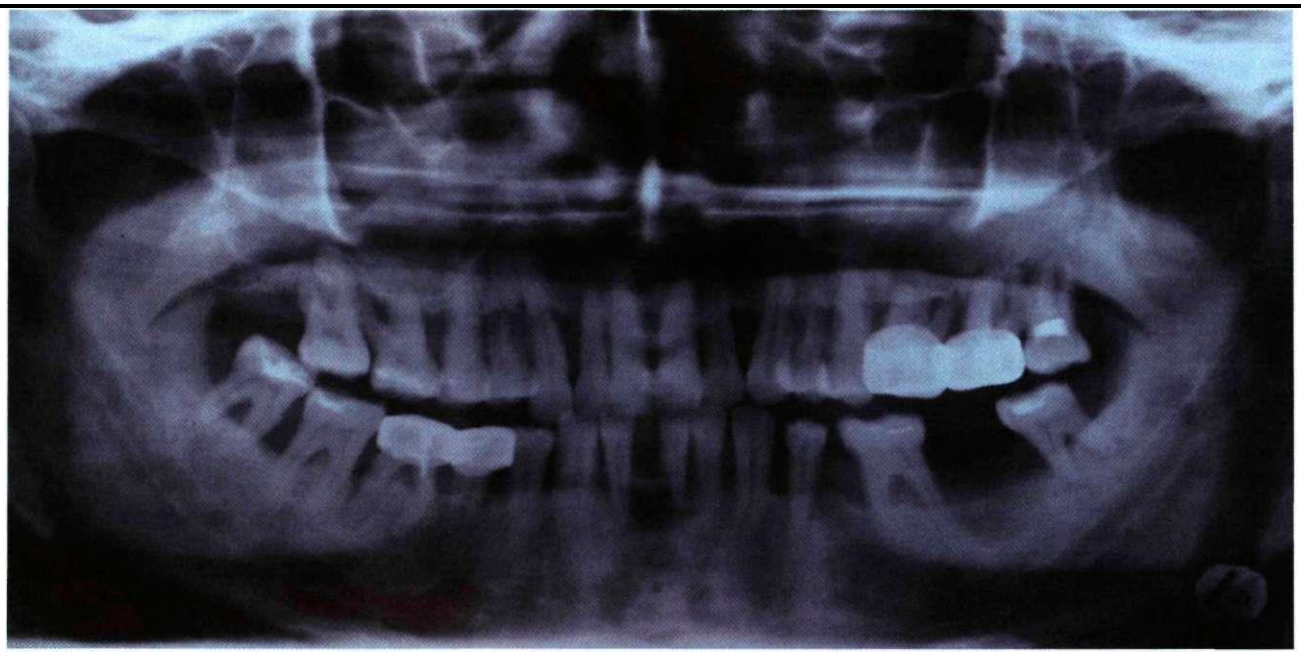
To summarise the material presented, it should be noted that a study of the bone condition of the alveolar portion of the jaws, based on the analysis of 104 orthopantomograms, in patients of both sexes with CTDnd 18 patients with ChGD without somatic pathologies, the following pattern was observed: alveolar bone resorption in the v/h and n/h regions of 30-37 year old women, which showed that bone loss was slightly faster in the v/h region (68%) than in the n/h region (48%) ($p<0.3$). It can be noted that the degree and magnitude of alveolar bone resorption of both jaws increases with age in patients with CTD abnormalities and the early onset of the disease - alveolar bone resorption is noted in the area of the maxilla. Also, our own R observations suggest that the presentation of the tissue state of periodontitis in CTD is specific, i.e. progressive disease and bone resorption is not always true. With or without hygiene regulations, most patients' bone changes remain stable for years, both quantitatively and qualitatively.

The results of a comparative analysis of the bone condition of the jaw with CTD and with ChGD, regardless of sex and age, show a

significant loss of interalveolar septal bone tissue, as measured by the Fuchs index in the range of 1/2 -2/3 of the root length, which corresponds to the severity of the disease. However, in younger patients (up to 30 years of age), alveolar bone resorption was selective and the highest level of resorption was observed in the masticatory teeth of the dentition and frontal groups of both jaws. The alveolar bone in the premolar region was almost intact. This is confirmed by the amount of bone resorption in the alveolar region of the jaw, as determined by the R-index. It should also be noted that the pattern of bone resorption, according to our observations, differed slightly between patients of different genders. On analysis of the results, the cortical index n/h may be an indicator of decreased BMD of the main skeleton. The minimal thickness of cortical layer was registered in patients with reduced skeletal BMD and was -5.8±0.4mm (group 1); -5.2±0.6mm ($p<0.001$) (group 2); -2.8±0.3mm ($p<0.001$) in the CG. By comparing the data obtained in the analysis of the cortical bone condition according to MCI in patients from the main comparison and control groups, we found that the width of the cortex n/h in all CGs was smaller than in groups 1 and 2. In order to examine the identified pattern, a regression and correlation analysis was previously carried out between the thickness of the cortex n/h and the number of filled teeth in men.

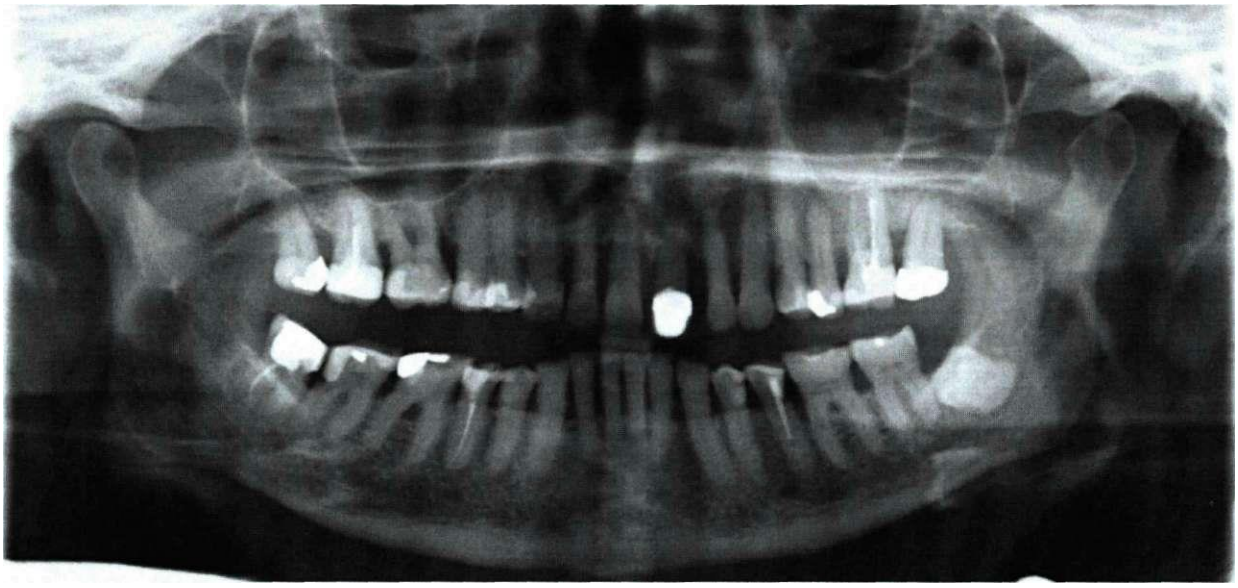
TableNº2.
Radiological evaluation of jaw bone condition depending on pathology

ndex indicator	Iarfan syndrome(1-group)	DCTD (Group2)	Ien Group 1 and 2	Vomen Group 1 and 2	-value of the Fisher criterion				
uchs index									
pper jaw	,48±0,02	,45±0,03	,38±0,04	,64 ±0,02		gr.	gr.	Iale.	emale
							.000	.000	.011
								.000	.003
									.002
ower jaw	,52±0,06	,51±0,04	,44±0,04	,78±0,06		gr .	gr.	gr.	gr.
							.000	.000	.000
								.000	.001
									.001
verallindicator	,50±0,05	,48±0,03	,36±0,02	,72 ±0,04		rp.	f.	gr.	gr.
							.000	.000	.000
								.796	.000
									.000
orticalindex									
	,8±0,4	,2±0,6	,4±0,1	,5±0,1		gr.	gr.	gr.	gr.
							.000	.672	.000
								.100	.000
									.078



Clinical example, orthopantomogram of patient K.N..

Patient K., 37 yearsold. (Male) Diagnosis: Marfan syndrome + aggravation of severe chronic generalised periodontitis.Has had bleeding gums since 10 years ago. Dairy products eaten regularly, never exercised. On examination, the POP is dark red, dry, lividity and pastosity of the gingival margin, pus in the area of all teeth. There is a periodontal abscess in the area of the lower central teeth. The bite cannot be determined due to the severe mobility of the teeth and changes in their position. KPU- index (C4; F8; E4). Hygiene index (H1)28.9; bleeding index (PB1) 4.8; gingival index (a) 3.0; tooth mobility 2.8; periodontal pocket depth 7.1mm. Radiograph description: Fuchs index for w/h-0.45; Fuchs index for n/h-0.58; MCI-4.8, cortical layer condition C1, radiological index for w/h-2.3 (89%); for n/h-1.94 (85%).



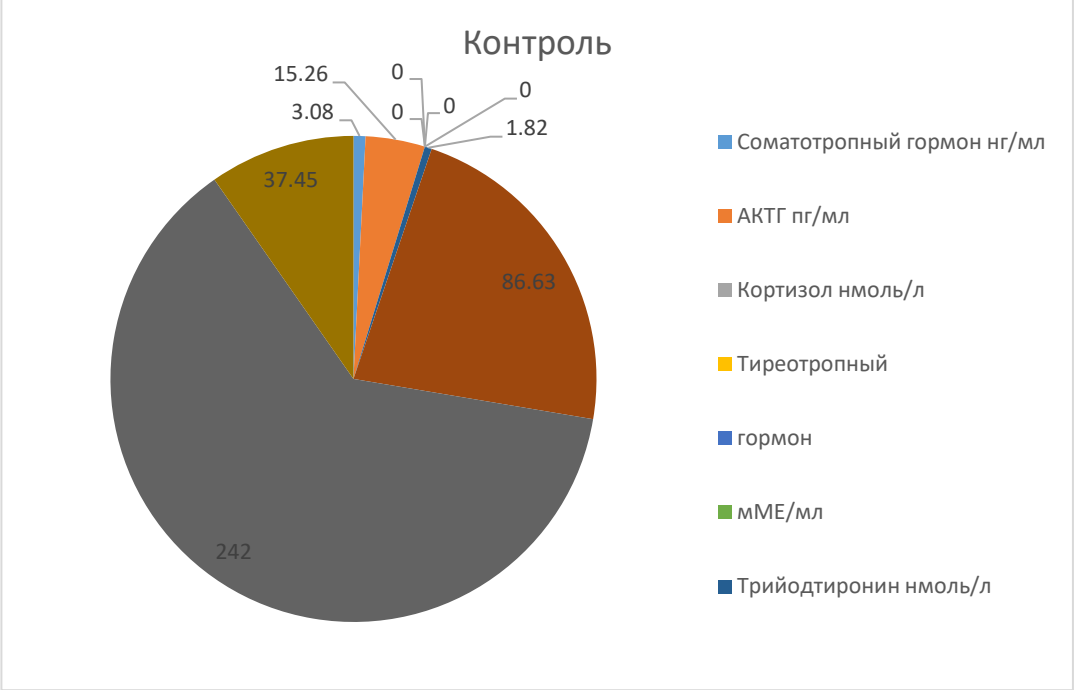
Patient A.Kh., age 35 (female). Diagnosis of UDCTD+ aggravation of severe chronic generalised periodontitis. According to the patient, about 20 years ago, her gums started bleeding. Now there is an aesthetic concern about a gap in my teeth. The oral cavity is pale,

thin, and there are dental impressions in the area of the occlusion. The gingival mucosa is hyperemic and swollen. Bite - prognathia, increased tooth wear, decreased bite height, fillings are not valid. KPU- *index (C2; F18; E2). Hygiene index (H1) 44.8; bleeding index (PB1) 2.4; gingival index (a) 2.6; tooth mobility 2.3; periodontal pocket depth 6.8 mm. Description of the radiograph: Fuchs index for w/h: 0.78; for n/h: 0.96; MC1-6.0; cortical layer condition C3, radiological index for w/h: 2.79 (79%); for n/h: 1.46 (42%).*

This, analysis of the R-weighted data for patients with CTD abnormalities shows that alveolar bone loss is more active, particularly of the horizontal type, predominantly in the interalveolar septa, whereas in CG patients with ChGD, vertical resorption with the formation of bone pockets predominates. It can be assumed that a decrease in BMD of the axial skeleton tissue (groups 1 and 2) influences the state of the bony part of the periodontium and can be attributed to risk factors for non-inflammatory periodontal pathology.

The results of the assessment of parathyroid hormone and electrolytes content in blood in patients with UDCTD averaged in women: Ca -2.44±0.12 mmol/l; P -1.67±0.4* mmol/l; Mg -0.78±0.08 mmol/l; P in urine -32.68±1.76 mmol/l/day, in men -2.391±0.12; -1.61±0.24; -0.88±0.04; -36.54±1.7 co-total: In women examined with Marfan syndrome in blood Ca -2.86±0.14; P -1.94±0.8*; Mg-0.66±0.14; in urine P -30.24±1.98; in men -2.44±0.1; -1.86±0.1*; -0.89±0.14; -33.73±1.86: Parathyroid hormone and electrolyte values in CG were -2.15±0.41; -1.24±0.14; -0.99±0.02; -38.4±2.25 respectively. Analysis of the results of the study states that the mean values of calcium, phosphorus and magnesium in males and females in Marfan syndrome and UDCTD in comparative assessment were not significantly different ($p>0.05$). It can therefore be assumed that the reduced parathyroid gland function in women with Marfan syndrome is not due to abnormal calcium-phosphorus metabolism but to genetically dependent dyshormonal changes. Relative to controls, serum magnesium was significantly reduced ($p<0.05$) and phosphorus was elevated, with patients with Marfan syndrome having higher levels than those with UDCTD.

In the results obtained on the effects on mineral metabolism of other hormones, we conducted an analytical evaluation of the hormonal profile in UDCTD depending on age and gender. Mean values in CG patients somatotropic hormone -3.08±0.22 ng/mL; ACTH -15.24±0.42 pg/mL; cortisol -490.0±22.12nmol/L; thyroid hormone -1.80±0.42 mU/mL; triiodothyronine -1.82±0.18 Nmol/L; thyroxine -86.63±1.22 nmol/L; prolactin-242.6±10.9 mU/mL; parathyroid hormone -37.45±1.12(pg/mL): CTD patients in the 18-20 age group were significantly higher -2.14; -18.24; -438.0; -1.72; -1.62; -96.45; -262.2; -44.29 ($p<0.05$) when compared with controls. This is obviously due to the fact that the growth process in this group of patients has not yet been completed, i.e. there is a direct correlation between the effect of somatotropic hormone on mineral metabolism in CTD. The absence of a hormonal shift in CG is due to completed biological growth.



In the graph above, we can see that a comparative assessment of the hormonal profile in CTD, depending on gender, showed that men with Marfan syndrome showed a significant increase in somatotropic hormone relative to women and the UDCTD and CG groups ($p<0.05$). The apparent high activity of the anterior pituitary lobe in men with Marfan syndrome is not due to sex differences, but to genetic determinants of CTD that remain unexplored. Women with Marfan syndrome, in contrast to men and individuals with UDCTD (male and female) and CG, showed low mean values of parathyroid hormone ($P<0.05$), which is the main mechanism of tissue BMD reduction in this disease.Also, plasma homocysteine levels in patients with hereditary CTD aged 18-20 years was -1.9±0.13 μmol/l; age 21-29 years was -26.57±0.14 and age 30-37 years was -32.61±0.11 μmol/l, while CG was -14±0.11 ($P2.3<0.05$). This indicates that there is no evidence-based difference between the reference limits of its variation, in age groups 1 and 2 ($p>0.05$)..Significant differences in homocysteine reference intervals were found between the 2nd and 3rd age groups in patients with Marfan syndrome and UDCTD ($p<0,05$). However, we know that the average homocysteine level increases by 3-5 μmol/l in both genders over the course of a lifetime.

At 40-42 years of age, men and women have a difference in homocysteine levels of about 2 μmol/l, with average concentrations of about 11 and 9 μmol/l, respectively.Comparative assessment of plasma homocysteine concentration in patients with Marfan syndrome in men -44.24±0.2*; in women -30.48±0.65; with UDCTD in men -32.86±0.21*; in women -22.61±0.44, while in CG patients -13.8±0.14 (*- $p<0.05$); results showed that the highest homocysteine concentration was found in men with Marfan syndrome. The reference limits of homocysteine fluctuations in men were significantly higher than in women in this group and in patients with UDCTD. It is possible that high homocysteine concentrations in patients with Marfan syndrome are mainly due to inheritance, i.e. homozygous cystathionine-3-synthase enzyme deficiency, characteristic of DCTD, and only to some extent related to gender. Homozygous deficiency of the enzyme cystatin-3 synthase results in impaired conversion of homocysteine to cystine, which is typical in Marfan syndrome [21]. Homocysteine levels in men with UDCTD were significantly higher than the mean homocysteine concentration not only in women in this group, but also in women with Marfan syndrome ($p<0.005$). Severe hyperhomocysteinemia can

be said to occur predominantly in a homozygous defect of the cystathion enzyme.

The following results were obtained from biochemical markers - bone formation and bone resorption, i.e., alkalin and osteocalcin in CTD aged 18-20 years osteocalcin -21.44±2.24 ng/ml; alkalin - 81.3±5.21 units/l; at 21-29 years -18.44±1.68; - 74.45±5.88; at 30-37 years -14.96±1.2; - 69.66±4.42 respectively.A comparative assessment of the mean values of AP and osteocalcin obtained from randomly selected patients aged 18-20 and 20-29 with CTD revealed no significant deviations of bone formation markers from the acceptable physiological variations in these parameters. ($p<0,05$). However, a more differentiated approach to analytical evaluation of bone formation markers with regard to genetic determinants showed that UDCTD (n=48) and Marfan syndrome (n=56) showed a high degree of quantitative differences in blood levels of AP and osteocalcin not only in relation to these parameters in controls, but also between groups 1 and 2 of the examinees; for UDCTD - AP -79.14±4.24 units/l for men and - 82.98±4.44 units/l for women; osteocalcin - 20.82±2.22*** ng/ml for men; 21.61±2.22** ng/ml for women: In Marfan syndrome - 126.22±10.66; -94.98±5.22; osteocalcin - 17.35±1.66*; -12.65±1.3 (*-$P<0.05$) respectively. From the results we can conclude that serum osteocalcin levels in the 18-20 age group correlate significantly with skeletal growth, which is due to puberty and hormonal instability.

However, significant differences in osteocalcin and AP levels depending on gender were found only in patients with UDCTD and in Marfan syndrome: UDCTD - AP-84.46±5.22d/l; osteocalcin -20.67±2.22 ng/mg***; Marfan syndrome -104.22±7.22*; -14.12±1.11**; in CG -70.44±2.22; -11.98±0.44 respectively. The results of the mean statistical data for osteocalcin and AP obtained in males and females with genetic UDCTD suggest that there are no gender differences in the process of bone formation ($p<0.05$). In men with Marfan syndrome, serum osteocalcin is significantly reduced not only with respect to CG data ($p<0.05$), but also with respect to those of women with the disease ($p<0.05$). The same changes were observed in AP content: its level in males was significantly higher than that in females and CG ($p<0.05$). However, it should be noted that serum AP levels were significantly higher in women with Marfan syndrome than in CG subjects ($p<0,05$).

Conclusion.Thus, the dental hard tissue condition on the background of reduced BMD is characterised by a high intensity of extracted teeth; also, in patients with CTD, specific changes characteristic of severe periodontal pathology are present in the periodontal tissues. However, the course of severe ChGD in young and middle-aged individuals has gender differences. In addition, these changes are seen in young and middle-aged patients without inflammatory periodontal disease, especially in patients with Marfan syndrome, which may serve as a diagnostic criterion for decreased BMD. An imbalance in the calcium-regulating hormone system in patients with CTD and UDCTD of middle age of both genders promotes the development of an aggressive course of the disease, which is determined by a reliably significant ($p<0.05$) deterioration of all periodontal indices, an increase in attachment loss and a greater degree of bone tissue resorption. It can be concluded that the mechanism of alveolar bone resorption in middle-aged patients with CTD is based on a disrupted bone remodelling cycle with an imbalance of calcium-regulating hormones.

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