Oral Conditions with Pathologies of Connective Tissue Dysplasia

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ABSTRACT

The study is based on retrospective and prospective data obtained by observing patients in 2016-2020 with varying degrees of connective tissue dysplasia who were under dispensary observation in the departments of the Republican Screening Centre of Uzbekistan and patients who applied for dental care at the clinic of the Centre for the Professional Development of Medical Staff with diagnoses of "differentiated and undifferentiated connective tissue dysplasia".

KEYWORDS: *Connective tissue dysplasia, osteogenesis imperfecta, Marfan syndrome, metabolic disorders.*

We know that connective tissue (CT) is a complex of mesenchymal derivatives consisting of cellular differons and a large amount of intercellular matter involved in the maintenance of homeostasis, whose polyfunctionality is determined by the complexity of its composition and organization. The CT has trophic, protective, supporting, plastic and morphogenetic functions [8, 9], and bone tissue is also considered to be a depot of calcium and phosphorus salts in the body [2]. Disorders of CT structure and metabolism are now regarded as CT dysplasia [3], which in most cases is systemic in nature, and it is shared during the embryonic and postnatal periods due to genetically altered fibrillogenesis of the noncellular matrix [10, 18], leading to disruption of homeostasis at the tissue, organ [22] and organismal levels and characterised by a progenerative course [19,20,].

Connective tissue dysplasia (CTD) reveals abnormal structure of collagen and elastin, glycoproteins, proteoglycans, and altered fibroblast function. A group of diseases called "mucopolysaccharidoses" is associated with abnormal metabolism of the main substance of CT. We know that molecular genetic techniques can be used to determine the structure and localization of genes responsible for the synthesis of various CT elements and how mutations in genes encoding elastin or collagen formation result in the formation of pathological trimmers of fibrous CT structures, leading to disruption of the structure and function of organs and systems [14].

A distinction is now made between differentiated and undifferentiated connective tissue dysplasia (DCTD and UDCTD) [19,20,]. DCTD is characterised by a specific type of inheritance, a distinct clinical picture, often established and well-studied genetic and/or biochemical defects such as Marfan, Ehlers-Danlos, Alport syndromes, osteogenesis imperfecta, bullous epidermolysis, etc.; UDCTD is diagnosed when a patient's phenotypic and other features do not fit into any of the differentiated diseases. Despite numerous publications on the problems associated with DCTD pathologies [19,20,], the topic of assessment and provision of specific dental care for these patients remains open, especially among children and adolescents who frequently seek dental care [10, 22, 8].

The aim of the study was to: an oral examination of differentiated (Marfan syndromes) and undifferentiated connective tissue dysplasias.

Materials and methods of research. The present study is based on retrospective data from 2016-2020 follow-up of patients with varying degrees of CT dysplasia who were under dispensary care at the Republican Screening Centre of Uzbekistan. We examined and analysed some data from the medical records of 56 people with hereditary CTD; 56 people with DCTD (Marfan syndrome); 48 people with UDCTD and 34 healthy individuals without signs of musculoskeletal dysplasia, aged 18 to 37 years, who sought dental care at the Centre for Health Professional Development Clinic (Table 1).

Table №1. Characteristics of those surveyed with DCTD pathologies and the control group by age and gender (M+n в %)

Diagnosis and groups	Gender	Age (M+n в %)		
M+n в %	M+n в %	18-20 лет	21-29 лет	30-37 лет
Marfan syndrome – 56/40,6 (Group 1)	Man– 32/57,1	8/25,0	13/40,6	11/34,4
	Woman- 24/42,8	6/25,0	10/41,7	8/33,3
UDCTD– 48/34,8 (Group 2)	Man – 25/52,1	7/28,0	11/44,0	7/28,0
	Woman- 23/47,9	7/30,4	10/43,5	6/26,1
Control group – 34/24,6 (CG)	Man– 15/44,1	5/33,3	5/33,3	5/33,3
	Woman- 19/55,9	7/36,8	5/26,3	7/36,8
Total – 138/100	Man – 72/52,2	20/27,8	29/40,3	23/31,9
	Woman- 66/47,8	20/30,3	25/37,9	21/31,8
Overall	138/100	40/29,0	54/39,1	44/31,2

The diagnosis of DCTD was made on the basis of a set of general clinical investigations: interview with the patient, general examination; instrumental (echodopplercardiography, computed tomography), 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 Yakovlev V.M., Nechaeva G.I. [19], all signs of dysplasticity-related changes in organs and systems were divided into: locomotor, cutaneous symptoms, visceral symptoms: In addition, micro features of impaired 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 frenum; and others. Various anthropometric methods were also used to verify the phenotypic features of DCTD. An important point for differential diagnosis was the collection and compilation of family genealogical history; in relatives of probands and healthy individuals were obtained by interview, direct examination of relatives if possible, and analysis of their medical records.

In order to assess bone mineral density (BMD), the trabecular and cortical bone mineral density was assessed using a computed tomography scanner: for this purpose, all patients underwent X-ray densitometry (DEXA) on a HOLOGIC Delphi-W densitometer in the lumbar spine at L4 and proximal femurs on the right and left; criteria were such indicators as bone mineral content - the amount of mineralised tissue in the scanned bone; bone mineral density - the amount of mineralised bone tissue in the scanned area and to assess the use of the T-criterion [4,12,]. In order to assess mineral metabolism and bone remodelling - bone formation and bone resorption in the CG of 12 men and 12 women, all were examined for mineral and bone metabolism.

All patients underwent general clinical examination; general blood and urine tests, biochemical and laboratory diagnostics were carried out on an analyser. Also, magnesium, calcium, inorganic phosphorus and alkaline phosphatase (ALP) activity in serum without any trace of haemolysis were determined. Normal values for total calcium in adult serum are 2.25-2.75 mmol/l, for magnesium 0.74-1.2 mmol/l, and for inorganic phosphorus 0.87-1.45 mmol/l. For urine calcium and phosphorus

levels, the normal concentration values were for inorganic phosphorus-13-42 mmol/24 hours, - calcium-2.5-7.5 mmol/24 hours. To examine patients' hormone profile, bone remodelling markers and homocysteine, the blood was collected on the day of blood sampling on an Immulite 2000 automatic analyser (Guttormsen A.B., Ueland P.M., Kruger W. et.al., 2001).

Also, serum levels of triiodothyronine, thyroxine, thyrotropic hormone, cortisol, parathyroid hormone, prolactin, adrenocorticotropic and somatotropic hormone in patients without traces of haemolysis were examined; The normal values were 9.5-65 ng/ml in adults, cortisol 138-635 nmol/l, thyroid hormone 0.4-4 mU/ml, somatotropic hormone in males 0-4 ng/ml, in females 0-18 ng/ml, adrenocorticotropic hormone <120 pg/ml, triiodothyronine 1.08-3.14 nmol/l, thyroxine 59-142 nmol/l.

The dental methods for assessment of dental hard tissue and periodontal condition, use the parameters of various indices taking into account the requirements of the International Protocol for the Assessment of the Severity of Periodontal Disease (NIDCR Protocol for Periodontal Disease Assessment) [8, 17, 18, 21], which include the following indices: - Caries affected (C), filled (P) and extracted (E) index, index calculation and caries intensity level were characterized according to 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 measures the presence or absence of soft plaque on all tooth surfaces. Also gingival index GI (Loe, Silness) - changes in the colour of the gum and the appearance of bleeding are obligatory signs of inflammatory periodontal disease; i.e.; 0 - normal gum; 1 - characterised by mild inflammation of the gum; 2 - gum is hyperemic, with bluish tint, moderate swelling and - 3 - pronounced hyperemia and swelling of the gum, tendency to spontaneous bleeding: The gingival papilla bleeding index PBI (Papilla Bleeding Index, Saxer and Mühlemann, modified by CowellL) was determined and scored; the periodontal pocket depth measurement and degree of attachment loss were examined using a button probe; the diagnosis of periodontal tissue pathology was made on the basis of ICD 10-C according to K05.31.

Radiological (R) methods - orthopantomography of the jaw bones was performed on an orthopantomograph. To quantify the degree of resorption of the alveolar portion of the mandible (n/h) and the alveolar process of the upper jaw (r/h), alveolar bone destruction indices - Fuchs index and R-cycle - were used. The MCI index was used to quantify and qualify the cortical layer of the n/h [4, 15, 19]. To assess the statistical significance of the results of the study, expressed in quantitative signs, we used analysis of variance, also assessing the statistical significance of the difference between group averages, using Fisher's test (F-criterion) when comparing more than two groups, Student's 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% ($p < 0.05$).

Results and discussion. We know that stimuli initiate the process of bone formation and bone resorption - still a subject of scientific debate. The concept of a stimulating and regulating effect of a number of osteotropic hormones on osteosynthesis is currently the most developed concept. The main ones are: parathyroid hormone, calcitonin, vitamin B-hormone, thyroid, gender and growth hormone. For comparison, the main quantitative indicators of mineral metabolism and regulatory hormones in practically healthy men and women aged 20-37 years, as we said investigated in 24 practically healthy people; results showed that calcium -2.50±0.41 mmol/l; phosphorus - 1.42±0.22 mmol/l and magnesium - 0.97±0.06 in blood and urine phosphorus - 37.2±2.35 mol/l in virtually healthy individuals aged 20-37 years:- Harmonal parameters - somatotropin 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±4.6 units/L; osteocalcin, 13.56±1.8 ng/ml; urinary deoxypyridinoline, 6.2±0.31 mol/creatinine daily; urinary calcium, 4.44±0.4 mmol/day; plasma homocysteine, 13.88±0.08 μmol/L.

As it is seen from the results, on the stomatological condition in the studied groups: in the 1st group - patients with Marfan syndrome, the intensity of caries is average -18,2±0,5; the ratio of KPU, C - 2,1±0,5; F-16,8±0,4; E-2,8±0,3 from total 24,7±0,4 teeth, thus the non-carious lesion of teeth was - 9,0±0,4; parodontal pathology -90,6±0,6. Among the patients of the group 2 - with DCTD pathology these figures 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 group 1, we can note that at the age of 18-20 the rates were: Caries -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 years 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, carious and non-carious dental hard tissue lesions and periodontal disease are in direct correlation, and their intensity increases with increasing age of patients. The same trend is observed in Group 2 patients; however, in the CG - i.e. totally healthy - a different trend is observed on the CT side of the subjects. The rates of carious and non-carious dental lesions and periodontal pathology were lower in CG patients than in Groups 1 and 2. The number of affected teeth with caries and extracted teeth, for caries complications, as well as the presence of periodontal disease were higher in group 1 than in group 2.

Table №2. Oral dental health of the target groups.

M+n в %	Age and quantity	Intensity Caries	Specific weight of the KPU				non-car. defeat. Teeth	Periodontal diseases
			C	F	E	Total teeth		
Syndome. Marfan – 56/40,6 (group 1)	14 лет 18-20	16,4±0,6	1,1±0,3	15,1±0,8	1,4±0,2	26,6±0,2	4,8±0,6	85,7±1,7
	21-29 years old– 23	18,6±0,6	2,1±0,4	17,1±0,4	2,6±0,4	24,8±0,2	8,8±0,4	91,3±1,2
	30-37 years old - 19	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
	Сред-е 18-37 лет	18,2±0,5	2,1±0,5	16,8±0,4	2,8±0,3	24,7±0,4	9,0±0,4	90,6±0,6
UDCTD– 48/34,8 (Group 2)	18-20 years old – 14	14,6±0,7	1,1±0,2	10,1±0,5	2,4±0,6	28,8±0,6	2,6±0,4	78,6±1,4
	21-29 лет – 21	17,2±0,6	2,1±0,6	14,1±0,6	3,2±0,2	26,6±0,4	4,4±0,8	85,7±1,6
	30-37 лет - 13	18,2±0,2	3,1±0,2	15,1±0,4	4,1±0,2	22,8±0,4	6,4±0,4	92,3±1,6
	Сред. 18-37 лет	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
Control group – 34/24,6 (CG)	18-20 лет – 12	10,3±0,4	1,2 ±0,3	8,4±0,2	1,1±0,1	25,8±0,4	2,1±0,8	58,3±1,8
	21-29 years old-10	12,3±0,8	1,2 ±0,3	8,6±0,2	1,6±0,1	24,8±0,2	2,2±0,8	60,0±1,4
	30-37 years old - 12	13,3±0,4	2,2 ±0,1	9,8±0,2	2,6±0,4	23,6±0,4	3,6±0,8	58,3±0,8
	Middle-aged 18-	11,96±0,6	1,5±0,3	8,9±0,3	1,8±0,6	24,71±0,8	2,6±0,6	58,8±0,6

	37 years							
Total by age. group – 138/100	18-20 years old – 40	13,7±0,5	1,13±0,4	11,2±0,4	1,6±0,2	27,2±0,6	3,2±0,6	74,2±1,2
	21-29 years old – 54	16,3±0,8	1,8±0,1	13,3±0,4	2,46±0,4	25,4±0,6	5,2±0,2	79,0±1,4
	30-37 years old - 44	17,03±0,8	2,8±0,1	15,6±0,1	3,7±0,1	23,0±0,8	7,8±0,4	81,8±0,8
Mid	138 people	15,7±0,8	1,9±0,3	13,4±0,4	2,6±0,8	25,2±0,6	5,4±0,4	78,3±1,2

The periodontal tissue index scores of the patients are shown in the table below №3.

Table №3. Hygiene assessment of the oral cavity and periodontal tissue condition, study group.

M+n в %	**Age and quantity**	**Hygiene index (H1)**	**Bleeding index (BI)**	**Gingival Index**	**Periodontal pocket depth (mm)**	**Magnitude of attachment loss (mm)**	**Tooth mobility**
Marfan syndrome. 56/40,6 (group 1)	18-20 years old – 14	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	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	16,4±2,1	3,0 ±0,1	3,0±0,2	8,8±0,6	10,0 ±0,8	3,0±0,4
	Сред-е – 18-37 лет	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 years old - 14	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 years old – 21	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 years old - 13	28,2±1,6	2,4 ±0,6	2,2±0,4	5,8±0,8	6,4 ±0,5	2,2±0,2
	Сред-е – 18-37 лет	31,9±1,5	1,9 ±0,3	1,9±0,5	4,5±0,7	5,6 ±0,4	1,6±0,6
Control group – 34/24,6 (CG)	18-20 years old – 12	62,3±1,6	0,5±0,1	0,3±0,1	0,5±0,1	0,8±0,1	-
	21-29 years old -10	67,8±1,4	0,6±0,1	0,8±0,1	0,9±0,1	1,1±0,1	-
	30-37 years old -12	68,3±2,1	0,4±0,1	0,3±0,1	0,8±0,1	1,1±0,1	-
	Сред-е- 18-37 лет	66,1±1,6	0,5±0,2	0,5±0,1	0,7±0,1	1,1±0,1	-
Total by age, group – 138/100	18-20 years old – 40	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 years old – 54	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 years old - 44	38,9±1,6	1,9±0,3	1,8±0,1	4,1±0,4	5,8±0,9	1,7±0,6
Mid	138 people	40,5±1,4	1,7±0,3	1,7±0,3	3,7±0,6	4,9±0,7	1,3±0,6

The comparative assessment of periodontal tissues between the sexes showed a statistically significant difference in all the studied indicators - women have more severe forms of inflammatory tissue lesions. According to the results shown in Table 3, the oral hygiene status of patients in groups 1 and 2 is understandable, both according to a number of literature data and according to the clinical condition of the patients [1, 5, 4, 16]. Analysing the hygienic state of the oral cavity in patients diagnosed with Marfan syndrome - the following parameters were observed: 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; while in patients diagnosed with DCTD these figures 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 CG-66.1±1.6, -0.5±0.2, -0.5±0.1, -1.7±0.1, no tooth mobility is noted, respectively. There is also a worsening of oral hygiene indicators in groups 1 and 2, directly related to age. Periodontal pocket depth was -5.4±0.1, 21-29 years -6.4±0.4, 30-37 years -8.8±0.6 in patients with Marfan syndrome and -3.2±0.1; -4.4±0.8; -5.8±0.8 in patients with DCTD pathology, respectively. According to the results of the data obtained, it can be concluded that with DCTD, patients have a greater damage to the organs and tissues of the oral cavity, both teeth and periodontal tissues, accompanied by severe bleeding and hyperemia of the gum tissues.

According to the results of the study of bone mineral density: the R-th index and the determination of the Fuchs bone number, the Fuchs index in patients of the 1st group averaged 0.48 ± 0.03, which corresponds to the degree of bone resorption of the alveolar part ranging from 1/ 2 to 2/3 the length of the root.

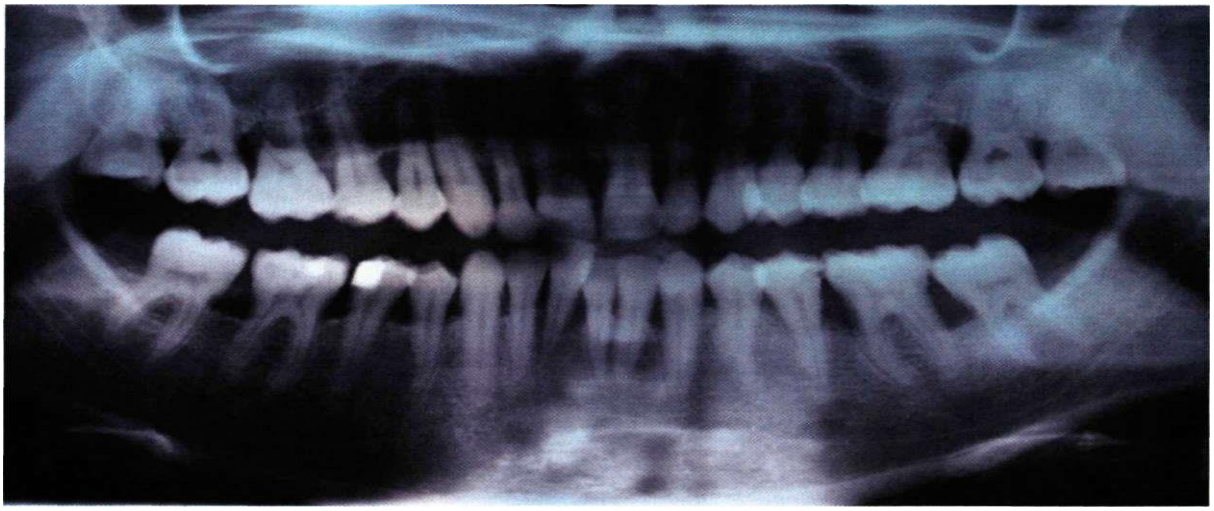
At the same time, the loss of bone tissue according to the R-th index turned out to be 1.54±0.08, which is 68% of the decrease in the total height of the alveolar process. The value of resorption of the bone tissue of the alveolar process in the h/h in patients of the 1st group was 1.88 ± 0.18 (72%), which turned out to be greater than the index for the h/h 1.72 ± 0.08 (65%) (p>0,2). The value of the Fuchs index, which determines the level of resorption, turned out to be almost the same on average (p>0.5) in both jaws. In order to study the features of bone resorption of the alveolar part of the jaws, in patients with different age groups, a comparative assessment of the state of the bone tissue was carried out, and there is a high sensitivity of the bone tissue to various external and internal influences, for example, a decrease in the functional load due to inflammatory diseases periodontal or violation of hormonal regulation of mineral metabolism, especially for patients of the 1st and 2nd groups. Spongy bone is more susceptible to such changes, marked by a shift in the remodeling process towards increased osteoclastic resorption, in contrast to cortical bone tissue, in which the rate of metabolic processes is 6-7 times lower than that of CG.

At the same time, the degree of loss of bone tissue of the alveolar process in the h/h practically did not depend on the age of patients in the CG, in contrast to the l/h, at 30-37 years, the level of resorption of the alveolar part was 0.22 ± 0.02 (up to 1/4 root length), which is almost 4 times lower than the Fuchs index from the 1st and 2nd groups up to 35 years 0.80±0.04 (up to 1/2 of the root length) (p <0.005). Hence, it can be concluded that with age, the loss of bone tissue in the alveolar part of the h/h in all patients with CTD occurs faster than in the alveolar process of the h/h. Analysis of the R-results of all groups confirms that the level of resorption of osteotropic hormones in patients with early onset CGP, the action of which enhances bone loss and reduces its MP.

Proven by many studies, a high correlation between the BMD of skeletal tissue and the MCI n/h index in various somatic pathologies makes it possible to use it as a dental criterion for reducing the BMD of the axial skeleton. Our results indicate the magnitude of resorption of the alveolar bone in/h

and n/h in patients aged 30-37 years showed that bone loss in the area of the alveolar process in/h occurs somewhat faster (68%) than in n/h (48%) ($p<0.3$). Thus, it should be noted that the degree and magnitude of resorption of the alveolar bone of both jaws in patients with CTD pathologies increases with age, and the early onset of the disease - resorption of the alveolar bone is noted in the area of the h/h.

Clinical example, orthopantomogram of patient K.Yu.



Drawing No. 1. Patient K., 36 years old. Diagnosis: Marfan syndrome. In the oral cavity, there is a rapidly progressive generalized periodontitis of severe form. From the anamnesis it follows that the patient was observed by a general practitioner-stomatologist at the place of residence for 8 years. Complaints during treatment: bleeding gums, tooth mobility, pain when eating and brushing teeth. For the first time, bleeding gums appeared at the age of 18. The results of the examination of the oral cavity: The mucous membrane of the oral cavity is red, dry. Small vestibule of the oral cavity, low attachment of the frenulum of the upper lip. Crowding of teeth in the anterior region. KPU index - 18.4; hygiene index - 28.2; bleeding index - 2.8; gingival index - 2.8; tooth mobility - 2.2; depth of periodontal pocket 6.8 mm. Description of the radiograph: Fuchs index for h/h - 0.5; for n/h -0.8; MS1-6.5, the state of the cortical layer C2, r - index for h/h-1.26 (76%); r - index for n/h-1.11 [8];

Thus, the analysis of R-data of patients with CTD pathologies - the loss of bone tissue of the alveolar bone is more active, especially in the horizontal type, mainly in the area of the interalveolar septa, while in CG patients with chronic pathology of periodontal tissues, the vertical nature of resorption predominates. with the formation of bone pockets. It can be assumed that a decrease in the BMD of the axial skeleton tissue [3, 7, 13, 15, 20,] (groups 1 and 2) affects the state of the periodontal bone and can be attributed to risk factors for the development of periodontal pathology of a non-inflammatory nature.

The results of assessing the blood levels of parathyroid hormone and electrolytes 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, respectively: Patients with Marfan's syndrome, in women in the 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. At the same time, the content of parathyroid hormones and electrolytes in the CG was - 2.15±0.41; - 1.24±0.14; - 0.99 ± 0.02; - 38.4 ± 2.25. Analysis of the results of the study shows that the average values of calcium, phosphorus and magnesium in men and women with Marfan's syndrome and UDCTD did not have significant differences in a comparative assessment ($p> 0,05$). Therefore, it can be assumed that the decrease in the function of the parathyroid glands in women with Marfan

syndrome is due not to calcium-phosphorus metabolism disorders, but to genetically dependent dyshormonal changes. In relation to the control, the content of magnesium in the blood serum was significantly reduced ($p<0.05$), and phosphorus was increased, moreover, in patients with Marfan's syndrome, the level of these indicators was more pronounced than in patients with UDCTD.

In the results obtained, on the effect on the mineral metabolism of other hormones in UDCTD, depending on age and gender, we carried out an analytical assessment of the hormonal profile. The average value in CG patients is somatotropic hormone -3.08±0.24 ng/ml; ACTH-15.24±0.42 pg/ml; cortisol -490.0±22.12 nmol/l; thyroid-stimulating hormone -1.80±0.42 mIU/ml; triiodothyronine -1.82±0.18 Nmol/l; thyroxine -86.63±1.22 nmol/l; prolacgin-242.6±10.9 mIU/ml; parathyroid hormone -37.45 ± 1.12 (pg / ml): in patients with CTD in the age group of 18-20 years, it turned out to be significantly more than -2.14; -18.24; -438.0; -1.72; -1.62; -96.45; -262.2; -44.29, respectively, when compared with CG ($p<0.05$). Obviously, this is due to the fact that the growth process in patients of this group has not yet been completed; there is a direct dependence of the effect of somatotropic hormone on mineral metabolism in CTD. The absence of a hormonal shift in CG was due to completed biological growth in both genders.

Table №4. Hormonal profile of patients with connective tissue dysplasia in men and women (M±м)

Studied indicators	Control	UCTD		Marfan syndrome	
		Men	Women	Мужчины	Women
Somatotropic hormone ng/ml	3,08±0,24	2,16±0,3	1,75±0,09	3,11±0,08*	2,01±0,1
ACTH pg/ml	15,26±0,42	18,91±1,4	16,45±0,9	24,32±1,7	15,95±0,8
Cortisolnmol/l	490,0±22,12	441,0±18,4	432,1±22,9	454,3±20,9	431,1±34,1
Thyrotrop. hormone. mIU/ml	1,80±0,42	1,75±0,07	1,82±0,09	1,91±0,08	1,67±0Д 1
Triiodothyronine mol/l	1,82±0,18	1,69±0,05	1,72±0,09	2,01±0,1	1,73±0,03
Thyroxine nmol/l	86,63±1,22	92,7±3,8	94,2±4,1	103,6±6,4	114,5±5,4
ProlactiimME/ml	242,6±10,9	238,8±16,2	269,0±10,1	251,8±9,89	216,5±14,1
Parathyroid. hormone (pg/ml)	37,45±1,12	39,41±1,86	36,49±1,01	33,97±1,99	28,80±0,94*

Appendix: *- $P<0.05$ in compared groups of men and women

The comparative assessment of the hormonal profile in CTD depending on gender shown in the table showed that in men with Marfan syndrome a significant increase in somatotropic hormone was found in relation to women and groups with UDCTD and CG. ($p<0,05$). The clearly high activity of the anterior pituitary gland in men with Marfan syndrome is not due to gender differences, but to the genetic determinants of CTD, which remain unexplored. In women with Marfan's syndrome, in contrast to men and individuals with UDCTD (men and women) and CG, low average values of parathyroid hormone ($P<0.05$), which is the main mechanism for reducing tissue BMD in this disease, were revealed.

The results of studying the age characteristics of the level of homocysteine in the blood plasma of patients with UDCTD in patients aged 18-20 years -21.9±0.13 μmol/l; at the age of 21-29 years -26.57±0.14 and at the age of -30-37 years was -32.61±0.11 μmol/l, while in the CG it was 14±0.11. ($P2,3 <0,05$). This indicates that there were no evidentiary differences between the reference limits of its fluctuations in the 1st and 2nd age groups ($p>0,05$). Significant differences in the reference intervals of homocysteine were found between the 2nd and 3rd age groups, in patients with Marfan

syndrome and UDCTD ($p<0,05$). At the same time, we know that during life the average level of homocysteine increases by 3-5 μmol/l in both genders. At the age of 40-42 years in men and women, the difference in homocysteine content is approximately 2 μmol/l with average concentrations of about 11 and 9 μmol/l, respectively. Therefore, the revealed difference in the distribution of homocysteine levels in blood plasma, taking into account age and gender in patients with CTD, is associated with genetic factors - homozygous and heterozygous deficiency of the enzyme cystathionine-3 - synthase, i.e. there is a violation of the conversion of homocysteine to cysteine.

The results of a comparative assessment of the concentration of homocysteine in blood plasma 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 patients of the control group - 13.8±0.14. (*-$p<0,05$). A comparative analysis of the level of homocysteine in blood plasma in men and women showed that the highest concentration was determined in men with Marfan syndrome.

The reference limits of homocysteine fluctuations in men were significantly higher than in women of this group, as well as in patients with UDCTD. It is possible that high concentrations of homocysteine in patients with Marfan syndrome are mainly due to the type of inheritance, i.e. homozygous deficiency of the enzyme cystathionine-3-synthase, which is characteristic of undifferentiated connective tissue dysplasia and is only to some extent associated with gender. With homozygous insufficiency of the enzyme cystatinin-3 synthase, there is a violation of the conversion of homocysteine to cystine, which is typical in Marfan's syndrome [11,19,20,].

In men with UDCTD, the level of homocysteine in the blood plasma significantly exceeded the average concentration of that not only in women of this group of patients, but also in women with Marfan syndrome ($p<0,005$). It can be said that severe hyperhomocysteinemia occurs mainly with a homozygous defect in the enzyme cystathionine (3-synthase) and is characteristic of DCTD, that is, Marfan syndrome and Ehlers-Danlos syndrome.

We have studied markers of bone formation and bone resorption, that is, ALP and osteocalcin in CTD dysplasia in age groups; at the age of 18-20 years osteocalcin -21.44±2.24 ng/ml; ALP - 81.3±5.21 units/l; at 21-29 years old -18.44±1.68; -74.45±5.88; at the age of 30-37 years -14.96±1.2; -69.66±4.42, respectively.

Comparative assessment of the average values of ALP and osteocalcin, obtained as a result of a random sample in patients aged 18–20 years and 20–29 years old with CTD, did not reveal significant deviations of bone formation markers from the allowable physiological fluctuations of these indicators ($p<0,05$). However, a more differentiated approach to the analytical assessment of bone formation markers, taking into account the genetic determinant, showed that in UDCTD (n=48) and Marfan syndrome (n=56) there are highly quantitative differences in the content of ALP and osteocalcin in the blood, not only in relation to of these indicators in the CG, but also between the groups 1 and 2 of examined; for UDCTD-ALP - 79.14±4.24 U/l for men and 82.98±4.44 U/l for women; osteocalcin -20.82±2.22***ng/ml for men; 21.61±2.22**ng/ml for women: with Marfan's Syndrome - ALP -126.22±10.66; -94.98±5.22; osteocalcin -17.35±1.66*; -12.65±1.3 (*-$P<0.05$), respectively. From the results obtained, it can be concluded that the level of serum osteocalcin in the age group of 18-20 years significantly correlates with skeletal growth, which is caused by puberty and hormonal instability.

At the same time, the content of osteocalcin and alkaline phosphatase, depending on gender, in patients with UDCTD and Marfan syndrome, significant differences were established only in genetic DCTD: ALP -84.46±5.22 units/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 average statistical data of osteocalcin and alkaline phosphatase, obtained in men and women with

genetic UDCTD, indicate the absence of gender differences in the process of bone formation ($p<0,05$).

In Marfan syndrome in men, serum osteocalcin is significantly reduced, not only in relation to the data of the control group ($p<0.05$), but also in women suffering from this disease ($p<0,05$). The same changes are observed when assessing the content of alkaline phosphatase: its level in blood serum in men significantly exceeded that in women and CG. ($p<0,05$). However, it should be noted that in women with Marfan syndrome, the level of ALP in the blood serum was significantly higher than in CG individuals ($p<0,05$). This means that the data obtained give us the opportunity to state that both men and women with Marfan syndrome have a violation of bone formation, which manifests itself with osteopenia of varying severity, which is consistent with the literature data [17,18, 19,21].

Conclusion. Thus, the state of hard dental tissues against 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 revealed high correlation dependence between the state of calcium homeostasis and the intensity of the carious process indicates the cause of secondary adentia in patients with reduced BMD of the skeleton - a violation of the mineralization of hard dental tissues. Also, in patients with CTD, there are changes in periodontal tissues that are characteristic of severe periodontal pathology.

At the same time, the course of severe ChGP in young and middle-aged people has gender differences. In addition, the high intensity of the carious process in young and middle-aged patients without inflammatory periodontal pathology, especially in Marfan syndromes, can serve as a diagnostic criterion for a decrease in BMD. Low BMD of the skeleton may be associated with the level of resorption of the bone tissue of the alveolar part of the jaws; the loss of alveolar bone in ChGP is more pronounced, in systemic osteoporosis and osteopenia, the loss of bone tissue of the alveolar process is generalized, uniform in the area of all teeth, while maintaining the shape of the interalveolar septa and the continuity of the cortical plate at the same time, on the orthopantomogram of the jaws on Against the background of the general porosity of the bone tissue, a clear pattern of bone trabeculae stands out.

An imbalance in the system of calcium regulating hormones in middle-aged patients with DCTD and UDCTD of both genders contributes to the development of an aggressive course of the disease, which is determined by a significantly significant ($p<0.05$) deterioration in all indicators of periodontal indices, an increase in attachment loss and a greater degree of bone tissue resorption.

The mechanism of bone tissue resorption of the alveolar process in middle-aged patients with CTD pathologies is based on a violation of the bone remodeling cycle against the background of an imbalance of calcium regulating hormones, while a decrease in the rate of bone formation against the background of a normal level of bone resorption is the cause of the development of pathology of teeth and tissues periodontal.

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