PREVALENCE AND CLINICAL - GENETIC FEATURES OF CONNECTIVE TISSUE DYSPLASIA IN THE UZBEK POPULATION

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Abstract *Experts in multiple fields (paediatricians, internists, rheumatologists, cardiologists, traumatologists, orthopaedists, gastroenterologists, neurologists, clinical geneticists, as well as general practitioners) must address the problem of connective tissue dysplasia. The clinical examination of patients reveals morphological changes that are accompanied by a range of clinical manifestations. These range from benign subclinical forms to progressive multi-organ and multi-system pathologies based on defects in collagen structure. These changes result in modifications to fibrous structures and the basic substance of connective tissue, which in turn cause structural and functional disorders affecting all organs. Determining the prevalence of this disorder, particularly in the Uzbek community, requires careful consideration of the genetic component of the illness. It should be highlighted that this issue has not received enough attention in the Uzbek public, and the information that is now available is dispersed and unhelpful.*

INTRODUCTION

Hereditary connective tissue dysplasia is a complex illness of the connective tissue that is linked together by shared exterior and visceral

features to form distinct syndromes and phenotypes. Recent studies have revealed that CTD is a pathological state brought on by a genetic abnormality of connective tissue production during the embryonic or postnatal stages rather than a syndrome or disease. All things considered, it drastically lowers the quality of life of patients and influences the progression of other illnesses, giving them a poor prognosis.

Mutations in enzyme genes involved in fibroblogenesis processes, or genes responsible for the synthesis and construction of the spatial structure of collagen and the generation of components of the intercellular matrix, are a major factor in the development of CTD. Now, a sizable subset of CTD genes has been elucidated. The majority of them are primarily monogenes and result from mutations in the genes that code for growth factor receptor genes, specifically fibroblast growth factor (TGF-β), MMP, and extracellular matrix proteins (collagens of different kinds, fibrillin, and tenascin). These pathological alterations may be primarily inherited with autosomal dominant or autosomal recessive patterns of inheritance, based on documented monogenic abnormalities of the extracellular matrix.

The purpose of the study is in order to maximize early diagnosis of the condition, the study set out to evaluate the incidence as well as the clinical and diagnostic characteristics of connective tissue dysplasia in the Uzbek populaion.

MATERIALS AND METHODS

In a population-based study, 221 individuals with CTD symptoms—90 (40.7%) men and 131 (59.3%) women—between the ages of 18 and 44 were included. Based on T.I. Kadurina's classification, a diagnosis was made. Forty generally healthy people (20.1±1.3) who provided informative verbal consent served as the control group for the comparative data. Due to a thorough analysis of anamnesis and instrumental examination, the examination group did not include individuals with concomitant pathology, namely those with rheumatism, cardiovascular illnesses, chronic liver, renal, or lung pathologies. On an empty stomach, blood was drawn from the ulnar vein in the morning for serum isolation, and Mg+2 ions (in mmol/L) were measured on the AF-610-The concentration of nitric oxide (μmol/L) for the two main stable metabolites, NO2 and NO3, was determined using an atomic absorption spectrophotometer (LTD, China). Using an automatic universal reader equipped with an AT-858 enzyme immunoassay analyzer (LTD, China), the following substances were identified: endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), endothelial and inducible NO synthase (eNOS and iNOS), peroxynitrite (ONO2-), and endothelin-1 (ET-1).

HLA titers and standard ELISA solid state ELISA kits from Human (Austria) were utilized. Class II typing was carried out by DNA amplification, and PCR was employed to identify the COL1A1 and MMP12 genes.

On Microsoft Windows, the acquired data were statistically processed using the Statistica 8 and Microsoft Excel 2013 software programs. The information is displayed as M±m. Student's t-criterion was used to determine the significance of differences, with $P < 0.05$ being considered significant.

RESULTS AND DISCUSSION

The Samarkand City Medical Association, Samarkand State Medical University Multiprofile Hospital, and Sharof Rashidov District Medical Association of the Jizzakh district served as the foundation for all clinical trials that were carried out between 2019 and 2022. There were 221 patients under observation in total, 90 (40.7%) male and 131 (59.3%) female. The patients' ages were as follows: 6.8% were under 20, 63.8% were between 19 and 32, and 29.4% were 33 and older. We conducted surveys with 2355 local individuals in the Samarkand and Jizzakh regions; 221 patients exhibiting indications of CTD were found among them. There was no discernible difference between the average incidence of CTD in Samarkand and Jizzakh, with 9.9% in Samarkand and 8.8% in Jizzakh, respectively, according to a review of patient data from both districts (Figure1).

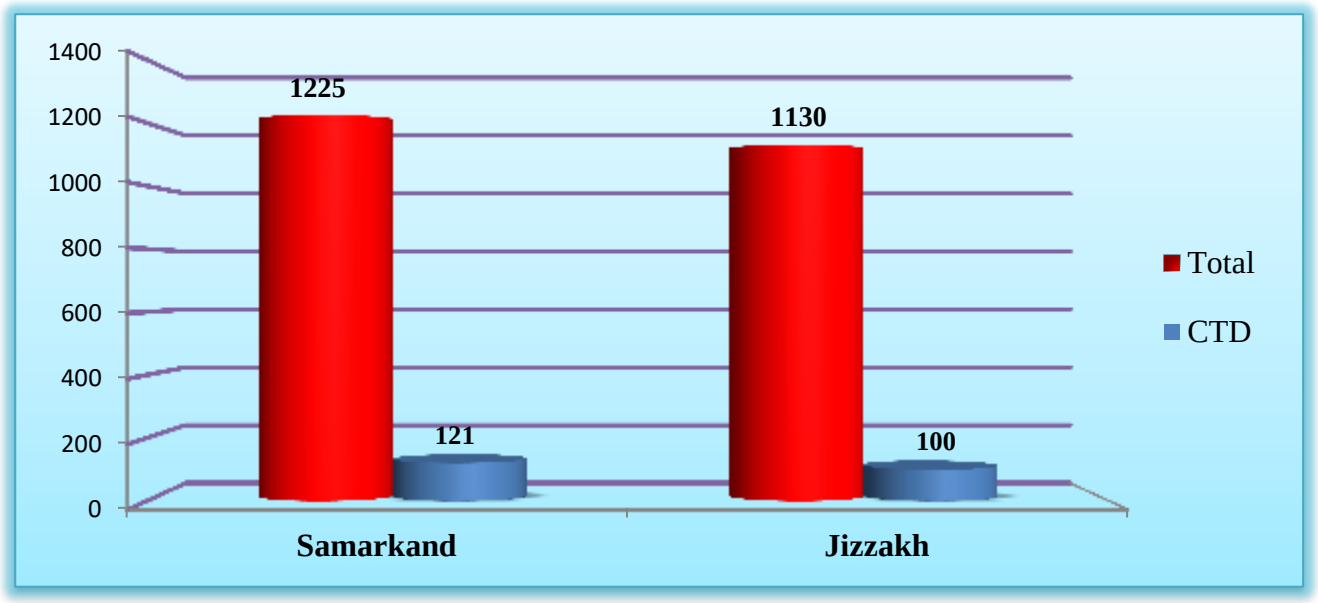

Figure 1. Incidence of CTD in the mentioned regions.

Patients were divided into 3 groups according to the severity of the disease:

Group 1 - mild course 96 patients (up to 3 signs of CTD)

Group 2 - moderate course 90 patients (up to 4-5 signs of CTD)

Group 3 - severe course 35 patients (more than 6 signs of CTD).

The distribution of patients according to age and sex is shown in Table 1.

Table 1. Distribution of CTD patients by age and sex

Age, years	**Women**		**Men**		**χ2**	**P**
	abs.	%	abs.	%		
Up to 18	9	4,1	6	2,7	0,48	>0,05
19-32	82	37,1	58	26,2	0,04	>0,05
Over 33	40	18,1	26	11,8	0,11	>0,05
Total	131	59,3	90	40,7	2,30	>0,05

According to the study, there was only a minor female predominance in the gender distribution of the patients, with males and females making up the majority. Additionally, we discovered that the condition was more common (63.8%) in the 19–32 age range.

Because the patients' age affected their height and weight, there were differences in BMI and other weight and height parameters among the study groups of patients. Anthropometric and phenotypic characteristics of the analyzed patients showed an average chest circumference of 85.46±7.25 cm, epigastric angle (in degrees) of 86.39±8.54, foot length as a function of height of 0.149±0.08, foot arch height of 7.65±1.15 cm, respectively.

Examining the prevalence of both internal and external phenomena in the patients in the comparison groups was our main goal. Table 2 shows the prevalence of musculoskeletal disorders.

Table 2. Incidence of musculoskeletal phenes

Phenes		1st group, n=96	2nd group, n=90	3rd group, n=35
Scoliosis (grades I and II)		39,6%	32,2%	34,3%
Kyphoscoliosis (grades I and II)		1,04%	11,11%	31,4%
Hyperlordosis		0%	8,89%	14,3%
Hypermobility of the joints	I	57,3%	48,9%	51,4%
	II	15,6%	22,2%	20%
	III	14,6%	21,1%	17,2%
	IV	3,13%	7,8%	11,4%
Flat feet	∑ of groups	17,65%	22,2%	22,9%
	Transverse	6,25%	6,6%	8,6%
	Longitudinal	11,4%,	15,6%	14,3%
Chest deformities		28,13%	31,1%	48,6%

Spinal abnormalities are one of the primary signs of CTD. A comparison group's incidence of bone and skeletal phenesis analysis showed that Groups 1 and 2 had 39.6% and 32.2% of patients with first- and second-degree scoliosis, 1.04% and 11.11% of patients with kyphoscoliosis, and 0% and 8.89% of patients with hyperlordosis, respectively. Patients in group 3 had hyperlordosis in 14.3% of instances, kyphoscoliosis in 11.42% of cases, and scoliosis in 34.29% of cases. The aforementioned data shows that group 1 had a higher frequency of spinal deformities, such as scoliosis of grades 1 and 2, but group 3 had complicated deformities, suggesting a more severe course.

Flat feet and hypermobility are signs of joint abnormalities in persons with CTD.

Of the individuals tested, all those in the second and third groups had hypermobility of varied degrees, while only 1/10 of those in the first group were free of this condition. Hypermobility of first, second, third, and fourth degree joints was thus found in 57.3%, 15.6%, 14.6%, and 3.13% of patients in Group 1, 48.9%, 22.2%, 21.1%, and 7.8% of patients in Group 2, and 51.4%, 20%, 17.4%, and 11.4% of patients in Group 3. It is noteworthy that the proportion of patients in each of the three groups showed a similar declining tendency based on how severe this phenomenon was. Revision of the criteria for separating the stages of hypermobility may be necessary due to the very narrow distribution of patients with the second and third degrees of hypermobility.

The data showed that the incidence of flat feet was 17.1%, 22.2%, and 22.9% in groups 1, 2, and 3. Concurrently, longitudinal flatfoot was found in 11.4%, 15.6%, and 14.3% of the individuals analyzed, and transverse flatfoot in 6.25%, 6.6%, and 8.6% of patients. The group differences were not statistically significant. There was no discernible variation in the incidence of flat feet between the comparative groups.

Chest deformities were present in 28.13% of Group 1 patients, according to an examination of their incidence. This category of clinical alterations was present in 31.1% of patients in group 2, but 48.6% of patients in group 3 exhibited chest abnormalities, a statistically significant increase from group 1 ($P<0.05$). Examining the thorax revealed that there was no statistically significant difference in the prevalence of the keel-shaped (pectus carinatum) and funnel-shaped (pectus excavatum) thorax deformities among the patients.

It can be inferred from the foregoing data that patients with CTD have distinct clinical variations of musculoskeletal lesions, which further

complicates the diagnosis process and treatment plan selection for therapists and general practitioners.

Analyzing the incidence of internal phenomena in CTD patients revealed that the development of varying degrees of myopia, which happened in about one-third of patients in all groups under comparison, was a defining feature of the disease's ocular manifestations. Nonetheless, it was evident that the degree of myopia correlated with the illness's severity. Therefore, 23 patients (23.96%) in group 1 had first-degree myopia, while 3 patients (3.1%) had second-degree myopia. The patients in this group did not exhibit retinal degeneration, astigmatism, or anisometropia. In 14.5% of group 2 patients ($P<0.01$), grade 1 myopia was detected, and in 15.6% ($P<0.01$), grade 2 myopia. Nevertheless, compared to the preceding two groups, a much lesser percentage of patients (2.8%) in Group 3 had first-degree myopia, while 20% had second-grade pathology. In addition to moderate to severe myopia, patients in this group had more severe and long-lasting pathogenic eye alterations, such as astigmatism (31.4%) and retinal degenerative abnormalities (28.6%). Group 2 patients were more likely to acquire ocular signs such as astigmatism and various degrees of myopia, whereas group 3 patients were more likely to experience more severe disruptions.

The existence of concurrent diseases or comorbidities further supported the frequent occurrence of internal phenotypes in our study patients, contingent on the severity of the ailment. Thus, among the patients in groups 1, 2, and 3, chronic bronchitis was found in 5.2%, 6.7%, and 11.4%; pyelonephritis in 6.25%, 7.8%, and 14.3%; biliary dyskinesia in 18.75%, 22.2%, and 31.4%; nephroptosis of both kidneys of the first and second degree in 6.3%, 12.2%, and 17.2%; and vegetative vascular dystonia in 49%, 62.2%, and 74.3%, respectively.

Of particular note are gastroduodenal pathology (5%), liver pathology (1.8%), lumbar spinal osteochondrosis (4.1%), anaemia (9.5%), osteoarthritis (6.8%) and others (n=221).

The statistically significant prevalence of comorbidities in group 3 patients compared to group 1-2 individuals indicated the preponderance of internal phenes in those patients.

Therefore, based on an analysis of the clinical manifestations of CTD, we can infer that the internal phenes of the condition were represented by abnormalities of the cardiovascular and pulmonary systems, abdominal and kidney organs, and most notably, the autonomic nervous system, while the

external phenes were characterized by small anomalies, skeletal, skin, and joint forms.

Disturbances in the morphological structure of connective tissue dysplasia, which is reflected by the extracellular matrix, collagen, and elastin, are one of the primary reasons of the disease's growing degenerative alterations. Prominent international scientists have recently highlighted the need of researching the regulation of magnesium ions, or extracellular matrix fibrillar proteins. A magnesium+2 deficit increases the risk of myxomatous degeneration of prolapsing mitral valve leaflets, cardiac rhythm abnormalities, and disruptions to the circulatory system, heart valve apparatus, and joints (16). In this context, we also looked into the amounts of oxyproline and magnesium in the serum of CTD patients. Research on this topic showed a propensity for blood magnesium levels to drop; in patients with comorbidities, particularly when combined with CTD, we found a considerable drop in magnesium content. Compared to values of basically healthy individuals, its blood serum level dropped by 1.2 times (P<0.001) in this patient group (Table 3).

Table 3. Serum Mg+2 ion, glucosaminoglycan, hyaluronidase levels and oxyproline excretion in CTD patients, M±m

Indicators	Control, n=20	1st group, n=96	2nd group, n=90	3rd group, n=35
Mg^{+2}, mol/l	0,912±0,022	0,902±0,022	0,759±0,038*^	0,623±0,038*^
Glucosaminoglycan, µmol/l	4,861±0,098	5,079±0,040	5,323±0,095*^	5,452±0,066*^
Hyaluronidase, µmol/l	203,50±2,04	211,00±7,60*	222,30±5,89*^	231,41±6,21*^
Total oxyproline, µmol/l	21,79±0,55	25,03±0,66*	27,09±0,42*^	29,02±0,52*^

* - p<0,05 compared to the control group,

^- p<0,05 compared to the patient group

Table 3's data indicates that low magnesium causes disease of the endothelium, abnormalities in the volumetric structure of collagen and elastin, and improper extracellular matrix component production. Therefore, if one considers that low magnesium causes endothelium damage, disorders of elastin and collagen organization that are responsible for the formation of extracellular matrix components, as well as enzymes involved in

the process of fibrillogenesis, one could assume that low magnesium in group 3 patients is one of the triggering mechanisms of collagen formation. In individuals with CTD, low magnesium levels may be a contributing cause to the pathology's clinical development. It's also important to note that, in the context of lower blood levels of Mg+2 ions, proteolytic enzyme activity has increased. In particular, total oxyproline excretion in subjects with CTD increased significantly by 14.9% in group 1, 24.3% in group 2, and 33.2% in group 3, relative to values in virtually healthy subjects.

Determining the severity of CTD is one of the most challenging aspects of therapy. Numerous writers credit this to the range of clinical presentations of CTD, which arise from the disease process involving multiple organs and systems, particularly the cardiovascular system. Numerous writers emphasize that endothelial dysfunction plays a major part in the development of CTD. The extracellular matrix protein genes' polymorphism is thought to be out of balance, according to the authors. There are also views that increased oxidative stress and decreased endotheliocyte nitric oxide generation locally are the causes of endothelial dysfunction (3,8). Impaired microcirculation, hypoxia, reperfusion, and the ensuing activation of vasculogenesis, angiogenesis, and the generation of vasoactive substances are hallmarks of endothelial dysfunction. The process involves the involvement of vascular endothelial growth factors, specifically VEGF (15, 16). Endothelial apoptosis is triggered by a reduction in VEGF in cells. Regression of vascular development and lumen blockage are the results of this procedure. In light of the aforementioned, we investigated the pro- and anti-angiogenic factor contents in DCF patients' serum based on the severity of heart valve regurgitation.

Research in this area revealed that patients' serum VEGF content had increased. The activation of vascularization processes was indicated by the fact that the content of this factor increased by 1.1 times in patients of Group I, 1.27 ($P<0.001$) times in patients of Group II, and 1.38 times in patients of Group III. The higher concentration of its receptors in the serum of the patients under examination serves as confirmation of this. Thus, to the first, second, and third groups, respectively, the content of VEGF-R1 increased in 1.2 ($P>0.05$), 1.42 ($P>0.05$), and 1.59 ($P<0.01$) times, and VEGF-R2 increased in 1.08, 1.18, and 1.24 ($P<0.05$) times (Table 4).

Table 4. Concentration of pro- and anti-angiogenic factors in serum of patients with CTD, M±m

№	1st group, n=96	2nd group, n=90	3rd group, n=35	Control, n=20

VEGF, ng/ml	151,92±2,58***	162,11±2,51***	176,13±2,98***^^^	138,58±1,69
VEGF-R1, ng/ml	0,610±0,055	0,700±0,049	0,799±0,038***^^	0,502±0,028
VEGF-R2, ng/ml	4,20±0,12	4,55±0,21	4,80±0,34*	3,879±0,265

Note: * - differences relative to the control group are significant (* - P<0,05, *** - P<0,001); ^ - differences relative to the group of Grade I patients are significant (^^ - P<0,01, ^^^ - P<0,001)

VEGF-R1 level variations were more noticeable, among other unique characteristics of these receptor alterations that we were able to identify. This is most likely caused by the specificity with which these receptors interact with growth factors. For instance, whereas VEGF-R2 only binds to VEGF, VEGF-R1 primarily binds to both VEGF and placental growth factor PIGF. HIV1 Tat is the inducer of VEGF-R2, which speeds up angiogenesis whereas VEGF-R1 inhibits it after attaching to VEGF.

An increase in endothelial permeability is one of the prerequisites for angiogenesis. The functions of the vascular endothelium include barrier, secretory, hemostatic, and vasotonic. It is crucial for both remodeling of the vascular wall and inflammatory responses. Nitric oxide, which is produced by the endothelium with the help of two distinct NO synthases, eNOS and iNOS, is primarily responsible for the increase in permeability. NO functions as a vasodilator, controlling arterial pressure and blood rheological characteristics, and is produced by endothelial cells and released into the bloodstream. In light of the aforementioned, we looked into a few NO system parameters in patients with varying degrees of regurgitation due to mitral valve prolapse, or MVP. The results revealed that in Group 1, Group 2, and Group 3, stable nitric oxide metabolites increased by 1.12 (P>0.05), 1.34 (P<0.001), and 1.41 times, respectively. The observed alterations are most likely the body's compensatory reaction to the existence of a particular type of chronic myocardial ischemia in this patient population. This is accompanied by a rise in the patients' serum VEGF levels, which causes some myocardial vascularization.

As a result, endothelial dysfunction in patients may be caused by an imbalance in the NO system. The overexpression of iNOS, the buildup of ONO2, and the suppression of eNOS activity are the causes of the imbalance in the NO system.

The polymorphism of the MMP12 and Col1A_1 genes as well as the diversity of the major histocompatibility complex (HLA) genes determine an individual's genetic susceptibility to and resistance to illnesses involving the synthesis of collagen. The Col1A_1 gene encodes the a1-chain of collagen type I, which is in charge of supporting and preserving a variety of bodily tissues, such as tendons, skin, cartilage, and sclera. The most prevalent type of collagen in the human body is type I collagen. The gene MMP12, which codes for the protein MMP12 (Macrophage Metal Elastase), is found on chromosome 11's short arm in the human genome. MMP12 substrate proteins include a variety of intercellular matrix proteins, such as type IV collagen of the major histocompatibility complex (HLA), and elastin, a connective tissue protein. The CC allele of the Col1A_1 gene and the AA allele of the MMP12 gene were found in the control group in our investigation on the frequency of these gene polymorphisms in members of the Uzbek community (figure 2).

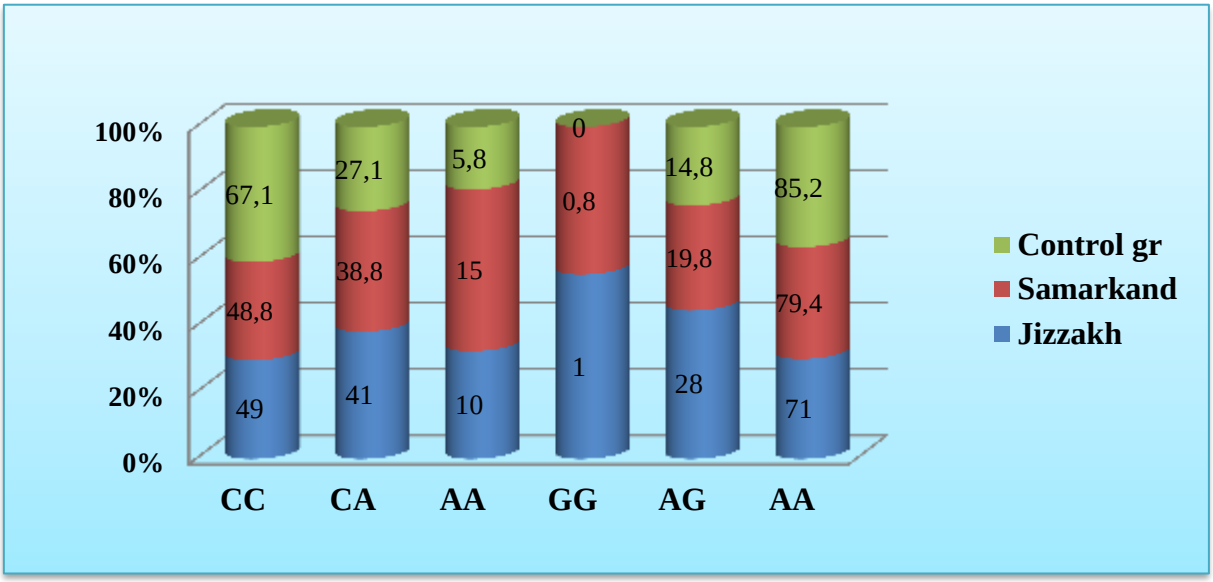

Figure. 2. The incidence of Col1A_1 and MMP12 polymorphisms in the Uzbek population among studied groups

The current investigation shown that the A allele (84.16%) accounts for the majority of the Col1A_1 genotype in CTD patients, both in terms of homozygous and heterozygous phenotypes. The Col1A_1 gene's AA genotype was linked to an expected risk (ER) of severe CTD (ER - 8.3, $p<0.001$), as shown in Table 2.

The A allele, which is more indicative of a homozygous genotype, is the main genotype for MMP12. Regarding the distribution of patients with

varying MMR12 genotypes, no variations were noted concerning the severity of CTD.

Significant differences in the frequency of different degrees of CTD were found between the groups based on the patient distribution according to Col1A_1 genotype (AA - 43.44%, AC - 40.72%, CC - 15.84%) (x2=70.20, p<0.001, Table 2). When homozygous and heterozygous patients were compared, differences were found between the AA and AC genotypes (H2 2H3=36.56, p<0.001), but not between the CC and AC genotypes (H2 2×3=4.02).

The frequency of HLA class II genes has been found to be statistically significantly higher in patients with CTD, especially in the first and second lines of consanguinity. An analysis was conducted on the frequency of class II HLA phenotypes in a group of patients with CTD and a control group. It was discovered that patients with CTD had a statistically significant increase in the frequency of class II HLA genes. Patients with CTD symptoms were the majority of those who carried the DQA1 gene allele 0501. Allele 0201 was found to be prevalent in patients with CTD, according to the interpretation of DQB1 HLA class II gene findings. Thus, it may be postulated that in order to further avoid CTD, all early diagnostic techniques should be used on patients who exhibit symptoms of the disease.

Therefore, it was found that CTD was positively correlated with higher RR values of the DQA1, DQB1, and DRB1 genes. Research has indicated that a higher frequency of these gene correlations was found in patients with myopia, flat feet, MVP, and myxomatous MV degeneration. This in turn implies that these tests can be used to accomplish early diagnosis and avert the development of potential problems.

We examined the heritable manifestation of CTD patients based on the disease's severity and looked at the patients' family trees in relation to the frequency of the illness's symptoms. Proband research demonstrated how genetic variables contribute to the development of CTD. Accordingly, if the frequency of incidence of CTD signs in the first, second, and third lineages was found in 11 (11.45%), 9 (9.4%), and 8 (8.3%) patients out of 96 patients in the first group of patients, then in Group 2 they were found in 13 (14.4%, P<0.01), 14 (15.6%, P<0.05), and 11 (12.2%, P<0.01) of 90 patients, and in Group 3 - in 12 (34.3%, P<0.01), 7 (20%, P<0.05), and 5 (14.3%, P<0.01) of 35 subjects.

CONCLUSION

The magnesium concentration investigation found that individuals with CTD in comparison groups tended to have lower concentrations of the

mineral, along with greater activity of proteolytic enzymes and excretion of total oxyproline, which may suggest a high degree of structural degeneration in the CT. The anatomical basis for the evolution of connective tissue disorganization in patients is endothelial dysfunction and activation of angiogenesis. The frequency and number of combinations of external phenoms, such as joint hypermobility (96%), changes in the spine (51.6%), thorax (32.6%), and flat feet (20.4%), and internal phenoms, such as myopia (28%), heart anomalies, and severe ECG and EchoCG rhythm disturbances, were associated with a higher degree of severity of clinical symptoms of CTD in group 3 patients. The current investigation showed that the A allele (84.16%) accounts for the majority of the Col1A_1 genotype in DST patients, both in terms of homozygous and heterozygous phenotypes. The Col1A_1 gene's AA genotype was linked to a significant DST OR (OR - 8.3, $p<0.001$). The A allele, which is more indicative of a homozygous genotype, is the main genotype for MMP12. Regarding the distribution of patients with varying MMR12 genotypes, no variations were noted concerning the severity of CTD. Additionally, patients with CTD showed favorable correlations with higher RR values of the DQA1, DQB1, and DRB1 genes. There is a connection between clinical manifestations of CTD, such as alterations in musculoskeletal and SSS phenotypes, and HLA class II genes (allelic variations of the DRB1 gene *14 and/or *15, 13/14).

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