JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS
VOLUME 05, ISSUE 01
MOPNTHLY JOURNALS
ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

THE ROLE OF REHABILITATION AND EXERCISE THERAPY IN IMPROVING CARDIOVASCULAR SYSTEM ADAPTATION IN CHILDREN WITH CONNECTIVE TISSUE DYSPLASIA

Mansuraliyeva Ziroat Shukurjon kizi
Master's student in Therapy (Traditional Medicine),Tashkent State Medical University.
E-mail:ziroat1000@gmail.com
ORCID ID: 0009-0006-1909-7019
Usmanxodjayeva Adibakhon Amirsaidovna
Doctor of Medical Sciences, Associate Professor, Head of the Department of Medical Rehabilitation, Sports Medicine, Traditional Medicine, and Physical Education, Tashkent State Medical University.
ORCID ID: 0000-0001-6124-6803

Abstract: The purpose of this study is to assess the level of adaptation of the cardiovascular system to physical exertion and the nature of its impairments in children with connective tissue dysplasia (CTD), as well as to determine the effectiveness of a complex of therapeutic physical exercises combined with rehabilitation measures. The study examines the impact of a rehabilitation-based approach on the functional parameters of the cardiovascular system, the degree of restoration of adaptation mechanisms, and the clinical significance of an individualized exercise program.

Conclusion: The obtained data indicate that in children with connective tissue dysplasia, the cardiovascular system demonstrates reduced adaptation to physical exertion. Rehabilitation measures, including dosed physical activity and breathing exercises, significantly improve this process, enhance cardiac functional capacity, and increase resistance to fatigue. A comprehensive approach improves the overall condition of the child and facilitates faster adaptation to daily activities.

Keywords: Connective tissue dysplasia, cardiovascular system, physical exertion, adaptation mechanisms, rehabilitation, exercise therapy, pediatric cardiology, integrative approach, recovery process.

Physical activity (PA) and physical fitness (PF) are considered important health-related indicators across all age groups, especially for children with chronic diseases [1]. PF is assessed using the Fitness Treadmill Test (FTT). The FTT is a graded treadmill test consisting of 90-second stages with progressively increasing speed and incline. After a warm-up period (3.5 km/h, 0% grade), the test begins at a speed of 3.5 km/h with a 1% incline, after which both speed (by 0.5 km/h) and incline (by 2%) are gradually increased until exhaustion occurs. Time to exhaustion (TTE) is defined as the moment when the participant stops the test despite verbal encouragement, excluding the 1.5-minute warm-up period. The FTT is well tolerated and provides reliable results in children aged 6–18 years [2]. Connective tissue dysplasia plays a significant role in the pathogenesis of diseases affecting the cardiovascular, respiratory, immune, and other body systems. The etiological and morphological aspects of the development of this pathology, its classification, as well as the clinical features of the course of certain diseases in both adults and children in the presence of connective tissue dysplasia, have been described. However, the relationship between external phenotypic signs of connective tissue dysplasia and the morphological and functional characteristics of internal organs has not been sufficiently

studied. The frequency and clinical significance of individual minor developmental anomalies, as well as the concordance between external manifestations of dysplastic syndrome and the nature and extent of involvement of the central and autonomic nervous systems and internal organs in systemic connective tissue pathology, remain unclear. Based on the above, further in-depth investigation of the role of connective tissue dysplasia in the formation and progression of internal organ diseases is required in order to improve early diagnosis, clinical assessment, prevention, and treatment of associated conditions [3]. Hereditary connective tissue disorders demonstrate similarities in physical characteristics that may develop during childhood. The extent to which children with hereditary connective tissue disorders experience disease burden remains unclear. This study aims to assess fatigue, pain, disability, and general health using standardized, validated questionnaires. Methods**.** This observational, multicenter study included 107 children aged 4–18 years with Marfan syndrome (MFS) (58%); Loeys–Dietz syndrome (LDS), 7%; Ehlers–Danlos syndromes (EDS), 8%; and hypermobile Ehlers–Danlos syndrome (hEDS), 27%. Assessments included PROMIS Fatigue Parent-Proxy and Pediatric Self-Report forms, pain and general health measured using a Visual Analog Scale (VAS), and the Childhood Health Assessment Questionnaire (CHAQ). Results**.** Compared with normative data, the total HCTD group demonstrated higher parent-reported fatigue T-scores ($M = 53$, $SD = 12$; $p = 0.004$, $d = 0.3$), higher pain VAS scores ($M = 2.8$, $SD = 3.1$; $p < 0.001$, $d = 1.8$), poorer general health scores ($p < 0.001$, $d = 2.04$), and higher CHAQ disability index scores ($M = 0.9$, $SD = 0.7$; $p < 0.001$, $d = 1.23$). Similar results were observed across HCTD subgroups. The most pronounced negative outcomes were found in children with hEDS, whereas the least severe outcomes were observed in those with MFS. Disability showed significant correlations with fatigue ($p < 0.001$, $r_s = 0.68$), pain ($p < 0.001$, $r_s = 0.64$), and general health ($p < 0.001$, $r_s = 0.59$).

Compared with normative data, children and adolescents with HCTD reported increased fatigue, pain, disability, and reduced overall health, with most differences representing large effect sizes. These novel findings highlight the need for systematic monitoring using standardized validated questionnaires, physical assessments, and tailored interventions integrated into clinical care [4]. Echocardiographic recordings of the heart and aorta were used to obtain cardiovascular parameters according to Lopez L, Colan SD, Frommelt PC, and Ensing GJ, including aortic diameters (mm) at the annulus, sinus of Valsalva (SoV), and ascending aorta; mitral valve prolapse (yes/no); severity of mitral insufficiency (MI); ejection fraction (%); left ventricular internal diameter in diastole (LVIDd, mm); and aortic insufficiency (AI). The Detroit nomogram was used to calculate Z-scores for the SoV and LVIDd, while the Halifax nomogram was applied to calculate the Z-score of the ascending aorta. In addition, heart rate, systolic and diastolic blood pressure, cardiovascular medications (CVM), aortic surgery (yes/no), date of surgery, and type of surgery were recorded. In children with MFS, the presence of systemic manifestations was assessed during physical examination using the systemic score of the revised Ghent criteria. Medical records were reviewed for a history of pneumothorax, dural medical records were reviewed for a history of dural ectasia and protrusio acetabuli.

The systemic score assigns points based on clinical features associated with MFS, including the wrist and/or thumb sign, pectus deformity, hindfoot deformity and/or pes planus, pneumothorax, dural ectasia, protrusio acetabuli, reduced upper-to-lower segment ratio and increased arm span-to-height ratio, scoliosis or thoracolumbar kyphosis, skin striae, myopia, and mitral valve prolapse [5]. Advances in medical and surgical care have significantly improved survival rates among children with congenital heart defects. However, survivors often experience reduced exercise capacity and health-related problems that negatively affect quality of life. Cardiac rehabilitation programs have been extensively studied in adults with heart disease. In contrast, studies involving children with congenital heart disease are scarce and limited. Therefore, we

conducted a systematic review of the literature on cardiac rehabilitation in children with congenital heart defects to evaluate existing evidence regarding utilization, effectiveness, benefits, and risks of this therapy, and to identify key components of successful programs [6]. Children and adolescents with congenital heart disease (CHD) should be encouraged to adopt an active lifestyle, ideally through participation in sports activities at school and in sports clubs. Children with complex cardiovascular conditions or additional risk factors (e.g., pacemakers, cardioverter-defibrillators, channelopathies) may require specialized, individualized exercise programs. This review article integrates current knowledge on the clinical effects of sports and exercise training on CHD and its underlying pathophysiological mechanisms. Studies involving a total of 3,256 patients with CHD were included, comprising 10 randomized controlled trials, 14 prospective interventional studies, and 9 observational studies, all aimed at improving physical activity, motor skills, exercise capacity, muscle function, and quality of life. Sports and exercise training appear to be effective and safe in patients with CHD. Despite being cost-effective, exercise programs are currently rarely reimbursed; Therefore, support from healthcare institutions, health commissioners, and research funding agencies is warranted. There is a substantial need to develop specialized rehabilitation programs for patients with complex cardiovascular diseases in order to improve access to this therapeutic intervention. Further studies may be required to validate these findings, assess their impact on risk profiles, and identify the most effective training methodologies and the underlying pathophysiological mechanisms [7]. Connective tissue dysplasia (hereditary collagenopathies) represents a genetically heterogeneous and clinically polymorphic group of pathological conditions associated with impaired formation of connective tissue during embryonic and postnatal development. Differentiated dysplasias include monogenic disorders with identified genetic defects and well-defined clinical features, such as Marfan syndrome, Ehlers–Danlos syndrome, and osteogenesis imperfecta. Undifferentiated hereditary dysplasia variants include primary mitral valve prolapse and other minor cardiac anomalies, tracheobronchial dyskinesia, visceroptosis, joint hypermobility, congenital chest wall deformities, “weakness” of the ligamentous apparatus of the lower limbs and spine, and other prevalological changes [8].

The aim of this study was to demonstrate the specific characteristics of cardiovascular involvement in connective tissue disorders through a group of fifteen cases followed over a ten-year period. The group consisted of eleven patients with Marfan syndrome (or Marfan-like syndrome), two with pseudoxanthoma elasticum, and two with Ehlers–Danlos disease. Cardiovascular lesions were as follows:

1. ascending aortic dissection confirmed and surgically treated in two cases;
2. aneurysmal dilatation of the ascending aorta in five cases;
3. isolated moderate mitral valve prolapse in two cases;
4. mitral valve dilatation in two cases;
5. mitral valve prolapse associated with tricuspid valve prolapse in one case, with severe mitral regurgitation necessitating mitral valve replacement;
6. in type I Ehlers–Danlos disease, moderate aortic valve aortic valve prolapse;

7) tetralogy of Fallot associated with Marfan syndrome, surgically treated in one case; 8) severe hypertension due to anomalies of the iliac and renal arteries in one case of pseudoxanthoma elasticum. Fatal complications occurred in three cases, including extensive dissection of the abdominal aorta and global refractory heart failure. In addition, twelve cases remained free of complications during a mean follow-up period of 3.5 years (range: 3–7 years) [9]. In the final part, we investigated the relationship between the severity of the cardiovascular phenotype in Marfan syndrome (MFS) and the type of FBN1 mutation. First, we examined the association between parameters of aortic stiffness (distensibility and pulse wave velocity measured by

magnetic resonance imaging) and the type of FBN1 mutation (nonsense or frameshift mutations due to in-frame or out-of-frame deletions/insertions). We were unable to demonstrate significant differences between these mutation types, suggesting that the FBN1 genotype alone is not the sole determinant of aortic stiffness. Second, we presented a detailed description of clinical findings in three unrelated MFS families showing remarkable intrafamilial phenotypic variability, providing further evidence of the lack of a clear genotype–phenotype correlation in MFS despite the presence of identified FBN1 mutations. This study also highlighted several important issues in MFS. First, repeated clinical evaluations of suspected patients may be necessary to establish an accurate and definitive diagnosis. Second, obtaining a comprehensive family history and performing clinical examinations of first-degree relatives can substantially contribute to diagnosis. Third, patients with "atypical" MFS phenotypes may show significant clinical overlap with other connective tissue disorders, such as Weill–Marchesani syndrome or Ehlers–Danlos syndrome, thereby increasing diagnostic complexity. We demonstrated that additional mutational analysis of the FBN1 gene can be a valuable tool in establishing the diagnosis and may assist in guiding medical management strategies in these challenging cases. In conclusion, we identified established diagnostic guidelines for the assessment of minor cardiovascular manifestations in MFS, and left ventricular dysfunction represents an important cardiovascular as part of the cardiovascular spectrum, indicating that left ventricular (LV) dysfunction should be monitored in the management of patients with MFS, and demonstrating that aortic wave reflection is not increased in MFS**.** In this study, we also examined genotype–phenotype correlations, highlighting significant (familial) variability in phenotypic expression and emphasizing the importance of molecular testing in the diagnosis of MFS. Overall, this article clearly demonstrates that close interaction and collaboration between cardiology and genetics provide added value in studying the disease pathogenesis of MFS and aortic aneurysms in general. We identified established diagnostic guidelines for the assessment of minor cardiovascular manifestations in MFS, showed that LV dysfunction is part of the cardiovascular spectrum and should be monitored in patients with MFS, and demonstrated that aortic wave reflection is not elevated in MFS. Furthermore, we investigated genotype–phenotype correlations, revealing substantial familial variability in phenotypic expression and underscoring the importance of molecular testing in the diagnosis of MFS [10]. Undifferentiated connective tissue dysplasia (UCTD) is one of the most common connective tissue disorders. The high prevalence of UCTD in the population and its potential role in triggering a wide range of other diseases make UCTD an important focus of modern biomedical research in cardiology, neurology, rheumatology, and pulmonology. Modern diagnostic approaches and identification of predisposition to UCTD contribute to the development of personalized therapies. In addition, magnesium-containing supplements and medications may be effectively used in the treatment of UCTD. In one of our previous studies, we analyzed possible molecular mechanisms underlying the etiology of UCTD, as well as the therapeutic effects of magnesium. The use of data on nucleotide polymorphisms as a complement to standard medical diagnostics represents a promising direction in post-genomic medical research. This study proposes a set of nucleotide polymorphisms that may be applied in the analysis of genetic associations in UCTD, as well as in evaluating the therapeutic efficacy of magnesium treatment. The selection and analysis of polymorphisms were based on criteria previously proposed by us using an integrated approach that included analysis of molecular mechanisms, comprehensive review of published data, and evaluation of the functional impact of nucleotide polymorphisms and the corresponding amino acid substitutions [11]. Connective tissue dysplasia (CTD) is a risk factor for musculoskeletal disorders. Structural alterations resulting from disorganization of collagen and elastin fibers lead to an inability to withstand significant mechanical stress. In clinical practice, the diagnosis of these conditions relies on

physical and anthropometric assessment. Forty-eight patients with frequent post-exercise musculoskeletal disorders were evaluated for CTD. The control group included 36 healthy participants. Both groups underwent anthropometric assessment and physical–physiological evaluation, including clinical examination, medical history, and anamnesis. Based on the examination results, study participants were assessed for the presence of CTD and associated risk factors. All patients in the experimental group had moderate to severe connective tissue dysplasia, with a mean total score of 49.44 ± 13.1. Several morphological features were found to be highly prevalent, allowing the identification of pathognomonic predictors of increased susceptibility to frequent post-exercise musculoskeletal disorders. Low back pain (100%), asthenic syndrome and kyphotic spinal deformity (75%), high-arched (gothic) palate, joint and auricular hypermobility, excessive tissue elasticity (63%), varicose veins of the lower extremities (56%) and hemorrhoids (56%), as well as alterations in foot and jaw morphology, indicate possible connective tissue dysplasia. The presence of these diagnostically significant morphological signs of CTD in individuals represents a pathognomonic predictor of increased susceptibility to injury. Early identification of these features may help to appropriately tailor physical activity regimens and develop targeted treatment strategies addressing the underlying cause [12]. Disorders of connective tissue (CT) formation result in significant pathological changes at both the level of individual organs and tissues and the organism as a whole. Diagnostic complexity, as well as the lack of unified terminology among physicians of different specialties, complicates the diagnostic is associated with the lack of a unified perspective on diagnostic criteria and the absence of a standardized diagnostic approach**.** The prevalence of external phenotypic signs of connective tissue dysplasia (CTD) is relatively high, which may lead to overdiagnosis. Conversely, insufficient attention to manifestations of CTD may result in delayed diagnosis, contributing to the development of complications. Clinical manifestations of dysplastic changes in the cardiovascular and musculoskeletal systems have been studied most extensively. This article provides an overview of available data on changes in the nervous system. Particular attention is given to nervous system pathology in differentiated forms of CTD, such as Marfan syndrome, Ehlers–Danlos syndrome, and others. Currently, the role of various vascular anomalies and aneurysms associated with undifferentiated forms of CTD is widely discussed. Considerable emphasis is also placed on clinical manifestations of the autonomic nervous system, with sympathetic nervous system predominance being characteristic of CTD. Evidence exists of an association between headaches, musculoskeletal pain, and CTD in both children and adults [13]. Connective tissue dysplasia (CTD) is increasingly studied as a pathology of hereditary morphogenetic origin characterized by multisystem clinical manifestations. This nonspecific syndrome leads to structural and functional abnormalities of collagen, elastin, and other connective tissue components in the pediatric population, resulting in widespread dysfunctions of the cardiovascular, respiratory, gastrointestinal, and musculoskeletal systems. In particular, delayed diagnosis and treatment during childhood lead to reduced quality of life, limitations in physical activity, and impaired social adaptation. Rehabilitation measures aimed at restoring function in children with CTD are currently regarded as one of the most important directions in modern medicine [14]. Health-related problems in patients with hereditary connective tissue disorders (HCTD) are diverse and complex and may result in reduced physical activity (PA) and physical fitness (PF). This study aims to investigate physical activity and physical fitness in children with hereditary connective tissue disorders (HCTD). Methods. PA was assessed using an accelerometer-based activity monitor (ActivPAL), and children's Mobility was assessed using the Pediatric Evaluation of Disability Inventory–Computer Adaptive Test (PEDI-CAT) mobility domain. Physical fitness (PF) was measured in terms of cardiovascular endurance using the Fitkids Treadmill Test (FTT); maximal handgrip strength (HGD) was used as an indicator of

muscular strength; and motor proficiency was assessed using the Bruininks–Oseretsky Test of Motor Proficiency, Second Edition (BOTMP-2). The study included a total of 56 children with a mean age of 11.6 years (interquartile range [IQR], 8.8–15.8) diagnosed with Marfan syndrome (MFS, n = 37), Loeys–Dietz syndrome (LDS, n = 6), and genetically confirmed Ehlers–Danlos syndromes (EDS, including classical EDS n = 10, vascular EDS n = 1, dermatosparaxis EDS n = 1, and arthrochalasia EDS n = 1). Regarding physical activity (PA), children with HCTD were active for a median of 4.5 hours/day (IQR 3.5–5.2), spent 9.2 hours/day (IQR 7.6–10.4) sedentary, slept 11.2 hours/day (IQR 9.5–11.5), and took a median of 8,351 steps/day (IQR 6,456.9–10,484.6). On the PEDI-CAT mobility domain, they obtained a below-average score (mean z-score -1.4 ± 1.6). In terms of physical fitness, children with HCTD performed well below average on the FTT (mean z-score -3.3 ± 3.2) and below average on the HGD (mean z-score -1.1 ± 1.2) compared to normative data. Conversely, BOTMP-2 scores were classified as average (mean z-score 0.02 ± 0.98). Moderate positive correlations were observed between PA and PF ($r(39) = .378$, $p < .001$). Moderate negative correlations were identified between pain intensity and both fatigue and time spent in activity (respectively, $r(35) = .408$, $p < .001$ and $r(24) = .395$, $p < .001$).

This study is the first to demonstrate reduced PA and PF in children with HCTD. Physical fitness correlated moderately positively with PA and negatively with pain intensity and fatigue. Decreased cardiovascular endurance, reduced muscle strength, and deconditioning, in combination with characteristic impairments of the cardiovascular and musculoskeletal systems, may contribute to these limitations. Identification of limitations in PA and PF provides a starting point for tailored interventions [15]. This experimental study focused on hereditary connective tissue disorders (HCTD), including Marfan syndrome (MFS), Loeys–Dietz For children with Loeys–Dietz syndrome (LDS) and Ehlers–Danlos syndromes (EDS), the feasibility, safety, and acceptability of a parent-involved physical activity program were evaluated. Secondly, the study aimed to explore preliminary observations regarding the program's effects on individual exercise goals and physical fitness, including aerobic and anaerobic capacity, strength, agility, pain, fatigue, and disability [16]. Children with HCTD may have specific health concerns (e.g., cardiovascular issues) that can influence participation in physical activity. Understanding these factors not only helps tailor interventions to meet the needs of children with HCTD but also informs the development of effective interventions in other populations. This study highlights the potential benefits of a tailored physical activity program for children with HCTD. Despite possible challenges, the intervention demonstrated feasibility and safety, and it provided a foundation for systematic evaluation of broader efficacy, including mechanisms for feedback to increase participant engagement. The physical activity program was successfully implemented in children with hereditary connective tissue disorders, supporting its potential in future studies. The intervention was safe, with no serious adverse events, reinforcing its suitability for subsequent research. Low participation rates indicate that strategies to enhance engagement will be important in future interventions. Preliminary observations suggest potential benefits in improving fitness and reducing symptoms, warranting further investigation. Health-related challenges in children with hereditary connective tissue disorders (HCTD) are characterized by multi-system involvement. The most common HCTD phenotypes, including Marfan syndrome (MFS), Loeys–Dietz syndrome (LDS), and Ehlers–Danlos syndromes (EDS), demonstrate musculoskeletal changes (e.g., scoliosis, foot deformities, and joint hypermobility), skin features (e.g., hyperextensible skin and tissue fragility), and cardiovascular problems (e.g., aortic aneurysm and mitral valve prolapse), with notable overlap particularly in MFS and LDS. Children with HCTD frequently experience fatigue, Children report difficulties participating in school, sports, and leisure activities alongside their peers due to pain and physical weakness.

Recent findings indicate that children with HCTD demonstrate lower endurance, muscle strength, and daily mobility compared with healthy peers. Despite a clear need for effective interventions, no multidisciplinary studies have targeted physical fitness in children with HCTD. However, previous research has shown that physical interventions in adolescents with generalized joint hypermobility (GJH) and hypermobile Ehlers–Danlos syndrome (hEDS) can yield positive outcomes, resulting in reduced disability and improved physical fitness. Additionally, combining physical training with cognitive-behavioral therapy focused on pain-related fear has been shown to enhance physical activity in this population. Parental involvement is crucial for fostering positive behavior changes related to pain management and fitness. Randomized controlled trials (RCTs) in hEDS have demonstrated significant improvements in pain and proprioception through various exercise modalities aimed at enhancing stability, muscle strength, and balance. Emerging exercise modalities such as functional power training (FPT) and high-intensity interval training (HIIT) have also been shown to improve muscle strength and exercise capacity in children with various chronic conditions. FPT enhances walking and lower extremity function through systematic resistance exercises and has been shown to be safe for children with disabilities. HIIT effectively improves aerobic capacity in children with conditions such as obesity and cerebral palsy. Given the lack of research on the feasibility, safety, and efficacy of FPT and HIIT in children with HCTD, this pilot intervention study was conducted to evaluate these parameters and provide valuable insights for future large-scale investigations. Assessing feasibility is essential to determine whether the intervention can be successfully implemented in a larger randomized controlled trial (RCT) for this specific population. The importance of pilot studies in intervention optimization is supported by research. Assessing acceptability ensures that the intervention is well-received by children and their parents, which is critical for adherence and long-term success. Safety is particularly important in this population, as children with HCTD are considered vulnerable, and providing evidence regarding the feasibility of implementation and potential impact on health outcomes facilitates the design of future studies. Therefore, the primary aim of this study was to evaluate the feasibility, safety, and acceptability of a physical therapy program for children with Marfan syndrome (MFS), Loeys–Dietz syndrome (LDS), and genetically confirmed Ehlers–Danlos syndrome (EDS), in conjunction with parent sessions. A secondary aim was to explore preliminary outcomes related to individual exercise goals, physical fitness (aerobic and anaerobic capacity, strength, and agility), as well as pain, fatigue, and disability. Pediatric populations have limited access to cardiac rehabilitation programs, and clinical research on this promising therapeutic approach is scarce. Questions regarding the optimal structure and effectiveness of these programs remain. The unique and complex needs of this population, in addition to the necessity of capturing additional outcomes beyond sequential cardiopulmonary exercise testing, require further in-depth analysis. Emerging concepts regarding joint hypermobility syndrome (JHS) and hypermobile Ehlers–Danlos syndrome (hEDS) phenotypes have raised multiple challenges related to classification, diagnosis, assessment, and management. Physical therapy within a multidisciplinary team plays a central role in managing individuals affected by hypermobility-related disorders. However, many physical therapists are unfamiliar with diagnostic criteria, prevalence, overall clinical presentation, and management strategies. The following guidelines aim to provide practitioners with the most current knowledge for assessing and managing children, adolescents, and adults with JHS/hEDS. Due to the complexity of symptoms within the JHS/hEDS profile, the International Classification of Functioning, Disability, and Health (ICF) framework is adopted as a central basis, where the general concept of disability encompasses functions, activities, and participation. the ICF framework is used to capture participation, as well as environmental and personal factors. Currently, the body of evidence on the management of JHS/hEDS is limited in both quantity and

quality, and there is insufficient research evaluating the clinical outcomes of various interventions. Multicenter randomized controlled trials (RCTs) are warranted to assess the clinical and economic effectiveness of interventions for both children and adults. Until such multicenter trials are conducted, clinical decision-making should be guided by theoretical reasoning and the best available limited evidence. International consensus and collaborative efforts to identify risk profiles for all individuals diagnosed with JHS/hEDS provide an opportunity to better understand pathological mechanisms and the potential to optimize health outcomes for affected individuals. [19] Connective tissue dysplasia (CTD) analysis in children with clinical manifestations focuses on the relationship between individual cardiovascular functional parameters and key biochemical markers. Among biochemical indicators of endothelial dysfunction (ED) in children with CTD, plasma nitric oxide (NO) levels are the most informative regarding the potential risk of developing ED. The maximal impact of ED in children with CTD manifests as impaired autonomic regulation, which is optimally assessed using the autonomic balance indices (LFn and HFn) from ECG evaluation via the PAC "Cardio-Pulse" system. Based on PAC Cardio-Pulse ECG assessments, an inverse correlation was observed between plasma vitamin D levels and the degree of autonomic dysfunction in children with CTD. ED in children with clinical signs of CTD contributes to the development of cardiometabolic disorders. Therefore, the presence of CTD constitutes an independent factor for impaired cardiovascular (CV) regulation in children, mediated through endothelial-dependent mechanisms controlling vascular tone and promoting secondary cardiometabolic changes. Accordingly, certain parameters from ECG and PAC Cardio-Pulse assessment—particularly the evaluation of T-wave symmetry and duration—may be considered as screening indicators for endothelial dysfunction in children with CTD and as markers for the further progression of cardiovascular pathology. Potential confounding factors may exist. The study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of each participating institution. Informed consent was obtained from all patients prior to participation. [20] Although antinuclear antibodies (ANA) are considered a key inclusion criterion for the diagnosis of undifferentiated connective tissue disease (UCTD), many patients exhibit variable ANA positivity and heterogeneous clinical presentations. The aim of this study was to re-evaluate UCTD diagnoses and analyze key predictors of disease evolution in a monocentric cohort. We retrospectively reviewed the records of 331 ANA-positive patients classified as UCTD between 2009 and 2017, all with at least one year of follow-up. The UCTD diagnosis was confirmed in 180 cases (54.4%). Disease evolution occurred in 18% of cases after a mean follow-up of 6.9 years (SD: 4.4). Raynaud phenomenon (RP) (OR: 2.39), swollen hands (OR: 6.3), anti-ENA antibodies (OR: 2.34), anti-topoisomerase I antibodies (OR: 4.93), and rheumatoid factor (RF) positivity (OR: 2.86) were significantly associated with disease evolution. Progression to systemic lupus erythematosus (SLE) occurred in 5 patients (2.78%), and was associated with the development of new autoantibodies compared to other disease evolutions (p: 0.034; OR: 12; 95% CI: 1.4–103.4). Evolution to systemic sclerosis (SSc) and primary Sjögren's syndrome (pSS) was observed in 14 (7.8%) and 8 (4.4%) patients, respectively. Swollen hands and RF positivity were predictive of SSc and pSS evolution, respectively. Among patients with confirmed UCTD, approximately half were evaluated according to standard criteria. The onset of hand swelling marked a potential evolution toward SSc, while the appearance of new disease-specific autoantibodies represented a characteristic "fingerprint" for patients progressing to SLE. [21] Undifferentiated connective tissue disease (UCTD) remains one of the most common diagnoses in routine rheumatology practice. Historical and recent data indicate that 20–50% of patients presenting to rheumatology clinics may receive a UCTD diagnosis. However, due to the lack of consensus definitions for UCTD, this term often

encompasses a wide spectrum of autoimmune and non-autoimmune clinical presentations. The clinical evaluation of these patients is therefore complex and requires careful longitudinal follow-up to identify patterns of disease evolution.

to analyze the characteristics and natural history of the disease, various authors have made multiple efforts to establish strict definitions of the disease, adjust the ANA (antinuclear antibody) titer thresholds, and modify inclusion criteria or follow-up durations. Globally, UCTD is considered a well-defined condition characterized by ANA positivity and the presence of one or more signs or symptoms of a defined connective tissue disease (CTD), to avoid misdiagnosis. Recently, some authors have proposed that UCTD could be viewed as a preclinical stage of CTD, defined by ANA positivity and specific inflammatory signaling or autoimmune activation pathways. This perspective suggests two main evolutionary profiles. Progressive development of new autoantibodies and the expression of interferon-related or fibroblast-activating cytokines may predict the onset of systemic lupus erythematosus (SLE) or systemic sclerosis (SSc), respectively. Currently, this approach is not routinely implemented for diagnostic purposes in most tertiary rheumatology centers. [22]

CONCLUSION

Connective tissue dysplasia (CTD) or undifferentiated connective tissue dysplasia (UCTD) is increasingly recognized as a broad clinical condition in modern medicine. Recent scientific research has repeatedly confirmed that this pathology is not merely a developmental or structural disorder, but rather a complex syndrome arising from the interplay of multiple regulatory systems within the body. Studies on the genetic basis, morphological features, clinical manifestations, systemic effects, diagnostic criteria, and therapeutic approaches of CTD have significantly expanded our understanding of this condition.

REFERENCES

1. Kotte EMW, de Groot JF, Bongers BC, Winkler AMF, Takken T. Fitkids treadmill test: normative values for Dutch children and adolescents according to age and sex. *Phys Ther.* 2016;96(11):1764–72. doi:10.2522/ptj.20150399
2. Bouchard C, Blair SN, Haskell WL, editors. *Physical activity and health.* 2nd ed. Champaign, IL: Human Kinetics; 2012.
3. Abduqodirova N. Bug‘uv to‘qinlari displaziyasi ba’zi tana tizimlari patologiyasini rivojlanishidagi element sifatida (adabiyot sharhi). *MDU [Internet]*. 2025 Feb 25 [cited 2025 Nov 24];(1):27-34. Available from: https://fdoctors.uz/index.php/journal/article/view/96
4. Loeys BL, Dietz HC, Braverman AC, et al. [Online]. Available from: https://www.mdpi.com/2073-4425/12/6/831
5. Loeys BL, Dietz HC, Braverman AC, Callewaert BL. [Online]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11035467/
6. Ubeda Tikkanen A, Rodriges Oyaga A. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/22251378/
7. Dold SK, Haas NA. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/36832425/
8. Simonenko VB, Dulin PA. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/16875074/
9. Bennis B, Mehadji BA. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/8517593/
10. De Backer J. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/20232788/

11. Torshin MI, Gromova OA. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/18991837/
12. Nikolenko VN, Oganesyan MV. [PubMed]. Available from: https://pubmed.ncbi.nlm.nih.gov/33032568/
13. Khaibullina DKh, Yesin RG. [Mediasphera]. Available from: https://www.mediasphera.ru/issues/zhurnal-nevrologii-i-psikhiatrii-im-s-s-korsakova/2023/7/1199772982023071007
14. Valiyeva MB, Sobirova GN. [Worldly Journals]. Available from: https://worldlyjournals.com/index.php/ituy/article/view/10358
15. de Koning L, Warnink-Kavelaars J. [ResearchGate]. Available from: https://www.researchgate.net/publication/369339366_Physical_activity_and_physical_fitness_in_children_with_heritable_connective_tissue_disorders
16. van Vulpen L, van der Xulst A. [Taylor & Francis Online]. Available from: https://www.tandfonline.com/doi/full/10.1080/09638288.2025.2467772#abstract
17. de Koning L, Warnink-Kavelaars J. [Taylor & Francis Online]. Available from: https://www.tandfonline.com/author/Warnink-Kavelaars%2C+Jessica
18. Ubeda Tikkanen A, Rodriges Oyaga A. [Cambridge Core]. Available from: https://www.cambridge.org/core/journals/cardiology-in-the-young/article/abs/paediatric-cardiac-rehabilitation-in-congenital-heart-disease-a-systematic-review/E04A0ACF723CC7A8D054F5B83B8C6AD4
19. Engelbert RH, Juul-Kristensen B, Pacey V. [Wiley Online Library]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31545
20. Oshlyanskaya EA, Ostapenko YuY, Chaykovskiy I. [Med-Expert]. Available from: https://med-expert.com.ua/journals/en/prevention-disorders-functional-state-cardiovascular-system-children-connective-tissue-dysplasia/