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CLASSICAL AND HYPERMOBILE EHLERS-DANLOS SYNDROME: A REVIEW OF COLLAGEN SYNTHESIS, CLINICAL MANIFESTATIONS, AND TREATMENT

EHLERS-DANLOS CLÁSSICO E HIPERMÓVEL: UMA REVISÃO SOBRE SÍNTESE DO COLÁGENO, SINTOMATOLOGIA E TRATAMENTO DA SÍNDROME

SÍNDROME DE EHLERS-DANLOS CLÁSICO E HIPERMÓVIL: UNA REVISIÓN SOBRE LA SÍNTESIS DE COLÁGENO, LA SINTOMATOLOGÍA Y EL TRATAMIENTO DEL SÍNDROME

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ABSTRACT

Ehlers-Danlos syndrome is a group of genetic disorders that affect collagen synthesis, leading to health complications and difficulties in daily life for those affected, including epithelial, intestinal, cardiac, psychiatric problems. Multisystemic condition that is underdiagnosed, managed primarily symptomatically, with no specific treatment available. This study reviews treatment options for cEDS and hEDS, addressing clinical manifestations and the genetic and pathophysiological mechanisms related to collagen instability, in order to evaluate therapeutic approaches aimed at improving cEDS and hEDS patients' quality of life. A literature review in which studies were analyzed from indexed databases, DeCS, Google Scholar, Orphanet, articles available on Ehlers-Danlos Society website. Information was extracted from the selected studies and synthesized. A total of 31 studies were included that identified the main complications of EDS and the role of vitamin C and protein supplementation in tissue repair. The methodological quality of the studies varied due to the lack of specific articles. One article was found that examined the relationship between vitamin C levels and hypermobility. Supplementation seems promising, but the absence of uniformity in protocols and need for further studies limit conclusions that can be drawn. There is evidence that more severe symptoms of EDS are related to tissue damage caused by structural changes in collagen. Muscle strengthening is essential for joint stabilization and non-pharmacological pain management, though analgesics should not be dismissed if necessary. Multidisciplinary care seems essential. Specific supplementation holds promise as a therapeutic approach to improving connective tissue health, with evidence suggesting that this combination may accelerate tissue repair.

KEYWORDS: *Ehlers-Danlos Syndrome. Classical Ehlers-Danlos Syndrome. Hypermobile Ehlers-Danlos Syndrome. Treatment of Ehlers-Danlos Syndrome. Vitamin C. Collagen. Muscle Injury. COL5A1. COL5A2. COL1A1. Hypermobility.*

RESUMO

Síndrome de Ehlers-Danlos (SED) é um conjunto de alterações genéticas que afetam a síntese do colágeno, acarretando agravos à saúde do portador e à sua vida diária, incluindo problemas epiteliais, intestinais, cardíacos e psiquiátricos. Condição multissistêmica, subdiagnosticada e de manejo predominantemente sintomático, sem tratamento específico. Revisão sobre as opções de tratamento da SED clássica e hipermóvel, compreendendo a síndrome, sintomatologia, mecanismos genéticos e fisiopatológicos que se relacionam à instabilidade do colágeno, avaliando opções de tratamento com finalidade da melhora da qualidade de vida dos indivíduos portadores da SEDc e SEDh.

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Revisão bibliográfica onde foram analisados estudos em bases de dados indexadas, DeCS, Google Acadêmico, Orphanet, artigos disponíveis no site Ehlers-Danlos Society. Informações destas bases de dados foram extraídas dos artigos e sintetizadas. Selecionaram-se 31 estudos que identificaram os principais agravos da SED, papel da suplementação da vitamina C e proteínas na reparação tecidual. A qualidade metodológica dos estudos foi variável, pela falta de artigos específicos. Encontrou-se 1 artigo relacionando níveis de vitamina C e hipermobilidade. A suplementação parece promissora, mas a falta de uniformidade nos protocolos e a necessidade de mais estudos limitam conclusões. Evidenciou-se que sintomas maiores da SED estão relacionados à lesão tecidual, causada pela alteração estrutural do colágeno. O reforço muscular é essencial para estabilização articular e manejo não farmacológico da dor, não dispensando analgésicos, se necessário. O cuidado multidisciplinar pareceu essencial. A suplementação específica tem potencial na abordagem terapêutica para melhora da saúde do tecido conjuntivo, com evidências sugerindo que essa combinação pode acelerar o reparo tecidual.

PALAVRAS-CHAVE: Síndrome de Ehlers-Danlos. Ehlers-Danlos Clássico. Ehlers-Danlos Hipermóvel. Tratamento na Síndrome de Ehlers-Danlos. Vitamina C. Colágeno. Lesão Muscular. COL5A1. COL5A2. COL1A1. Hipermobilidade.

RESUMEN

SED es un conjunto de alteraciones genéticas que afectan la síntesis del colágeno provocando problemas y dificultades en la vida cotidiana, incluyendo trastornos epiteliales, intestinales, cardíacos y psiquiátricos. Es una condición multisistémica, infradiagnosticada y cuyo manejo es predominantemente sintomático, sin un tratamiento específico. Revisión de las opciones de tratamiento para SEDc y SEDh, comprendiendo el síndrome, sintomatología, mecanismos genéticos y fisiopatológicos relacionados con inestabilidad del colágeno, evaluando opciones de tratamiento con objetivo de mejorar la calidad de vida de personas con SEDc y SEDh. Revisión bibliográfica que se analizaron estudios procedentes de bases de datos indexadas, DeCS, Google Académico, Orphanet, artículos disponibles en website Ehlers-Danlos Society. Las informaciones han sido extraídas y sintetizadas. Se seleccionaron 31 estudios que identificaron las principales complicaciones del SED, el papel de suplementos de vitamina C y proteínas en la reparación tisular. La calidad metodológica de los estudios fue variable, por falta de artículos específicos. Se encontró 1 artículo relacionando niveles de vitamina C y hipermovilidad. La suplementación parece prometedora, pero la falta de uniformidad en protocolos y necesidad de más estudios limitan conclusiones. Se demostró que síntomas más graves del SED están relacionados con la lesión tisular, causada por alteración estructural del colágeno. El fortalecimiento muscular es esencial, así como el manejo no farmacológico del dolor, sin descartar el uso de analgésicos si es necesario. Atención multidisciplinaria se consideró esencial. La suplementación específica tiene potencial en el enfoque terapéutico mejorando la salud del tejido conjuntivo, hay evidencia que sugiere que esta combinación puede acelerar la reparación tisular.

***PALABRAS-CLAVE**: Síndrome de Ehlers-Danlos. Ehlers-Danlos clásico. Ehlers-Danlos hipermóvil. Tratamiento del síndrome de Ehlers-Danlos. Vitamina C. Colágeno. Lesión muscular. COL5A1. COL5A2. COL1A1. Hipermovilidad.*

INTRODUCTION

Ehlers-Danlos Syndrome (EDS) is a group of genetic disorders that affect collagen synthesis, causing connective tissue problems, and which has 13 subtypes (1). In Classical Ehlers-Danlos Syndrome (cEDS) mutations in the COL5A1 and COL5A2 genes, located on chromosome 9, are implicated, affecting the production of type V and type I collagen, respectively. However, until the date of this review, no associated genes have been identified for hypermobile Ehlers-Danlos syndrome (hEDS) (2).

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EDS, classified under ICD-10 code Q79.6 (3), is characterized by a condition that affects collagen synthesis, resulting in symptoms such as joint hypermobility, skin hyperelasticity, and muscle and vascular fragility, as well as intestinal and urinary complications (4).

cEDS and hEDS cause many health complications for patients, as well as difficulties in their daily lives, including epithelial, intestinal, and cardiac problems, as well as mood fluctuations. However, there is no specific treatment, and management is generally symptomatic (5).

Ehlers-Danlos Syndrome is diagnosed through medical history and clinical evaluation, including a specific physical examination using the Beighton scale, and by exclusion, when the individual presents signs of joint hypermobility that cannot be attributed to other conditions. During the evaluation, it is necessary to rule out other conditions that may cause similar symptoms.

It is a hard-to-diagnose condition that is usually confused with other diseases (6) due to its complex and nonspecific symptoms. It receives constant updates and remains largely underdiagnosed, with a direct impact on the individual's life quality (1).

Currently, the prevalence of cEDS is 1 to 9 per 100,000 individuals (7) and is still considered rare, but some authors believe it is underreported and may affect 1 in every 600 to 900 people (4), rendering the diagnosis challenging and delayed.

In order to discuss the therapeutic approach, it is essential to first understand the syndrome, definition, classification, symptoms, comorbidities, diagnostic errors, biochemical and pathophysiological disorders associated with the syndrome.

Nutritional supplementation is rarely discussed and is even underestimated in the treatment of Ehlers-Danlos syndrome (EDS). Quispe Pari (8, p. 1) says that systemic impairment in patients who have Ehlers-Danlos syndrome stems from enzymatic dysfunctions responsible for collagen biosynthesis, given that these proteins are essential in all connective tissues. (8)

Vitamin C performs a crucial role in collagen synthesis, acting as a cofactor in the hydroxylation reactions necessary for the molecule's stability (9), and it is essential to understand this biochemical process in order to comprehend the pathophysiology of the syndrome. Low levels of this vitamin have direct effects on collagen, which negatively impacts the formation of new blood vessels and the skin healing process (10). This matter is particularly relevant for individuals with EDS, where investigations into genetic polymorphisms that influence vitamin C levels could elucidate the relationship between the phenotypic manifestations of cEDS and hEDS.

Considering the 13 subtypes of Ehlers-Danlos syndrome (EDS), which affect different types of collagen, this review focuses only on the genetic and biochemical causes related to Classical Ehlers-Danlos Syndrome (cEDS) (COL5A1 and COL5A2 genes) and Hypermobile Ehlers-Danlos Syndrome (hEDS) (no associated gene) (2), whose clinical manifestations are similar, and in which possible treatments for the syndrome were investigated based on collagen structure and the genes involved in this process, investigating the interactions between collagen synthesis, vitamin C, and genetic variants. The

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study evaluates the role of vitamin C in EDS, the efficacy of nutritional supplementation and multidisciplinary approaches to improve clinical management and patients' life quality, with a focus on the pathophysiological mechanisms shared among these subtypes.

A dissociation is observed between the multisystemic complexity of EDS and the fragmentation of available therapeutic approaches. Furthermore, there is a gap in the evaluation of the efficacy of available treatment options, which range from symptomatic interventions to multidisciplinary approaches that lack standardization or specific guidelines.

The matter revolves around whether hypermobile Ehlers-Danlos syndrome (hEDS) constitutes a genetically distinct entity or can be explained, even if only partially, by polymorphisms in genes that regulate vitamin C metabolism (an essential cofactor for collagen stabilization), which calls for the development of personalized clinical management strategies based on pathophysiological mechanisms, moving beyond the current paradigm of purely symptomatic and empirically fragmented interventions.

THEORETICAL FRAMEWORK

Definition of Ehlers-Danlos Syndrome (EDS)

Ehlers-Danlos syndrome (EDS) comprises a group of connective tissue disorders caused by abnormalities in collagen production and organization, with 13 recognized variants (1). The classical form (cEDS) has a well-defined genetic basis, associated with mutations in the COL5A1, COL5A2, and COL1A1 genes on chromosome 9, which impairs the synthesis of type V collagen and, consequently, type I collagen (1). Currently, the prevalence of cEDS is 1 to 9 per 100,000 individuals (7), and it is still considered rare. However, some authors consider it underreported, with a prevalence potentially reaching 1 in every 600 to 900 people (4).

EDS classification

The 2017 international classification of Ehlers-Danlos syndrome recognizes 13 subtypes and proposes a clinical classification with new descriptors that encompass characteristic manifestations of the phenotype, rather than relying solely on genetic classification. (2)

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Image 1. Clinical Classification of the Ehlers-Danlos Syndrome, Inheritance Pattern and Genetic Basis

TABLE I. Clinical Classification of the Ehlers-Danlos Syndromes, Inheritance Pattern, and Genetic Basis

	Clinical EDS subtype	Abbreviation	IP	Genetic basis	Protein
1	Classical EDS	cEDS	AD	Major: *COL5A1, COL5A1* Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type V collagen Type I collagen
2	Classical-like EDS	clEDS	AR	*TNXB*	Tenascin XB
3	Cardiac-valvular	cvEDS	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
4	Vascular EDS	vEDS	AD	Major: *COL3A1* Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys)	Type III collagen Type I collagen
5	Hypermobile EDS	hEDS	AD	Unknown	Unknown
6	Arthrochalasia EDS	aEDS	AD	*COL1A1, COL1A2*	Type I collagen
7	Dermatosparaxis EDS	dEDS	AR	*ADAMTS2*	ADAMTS-2
8	Kyphoscoliotic EDS	kEDS	AR	*PLOD1* *FKBP14*	LH1 FKBP22
9	Brittle Cornea syndrome	BCS	AR	*ZNF469* *PRDM5*	ZNF469 PRDM5
10	Spondylodysplastic EDS	spEDS	AR	*B4GALT7* *B3GALT6* *SLC39A13*	β4GalT7 β3GalT6 ZIP13
11	Musculocontractural EDS	mcEDS	AR	*CHST14* *DSE*	D4ST1 DSE
12	Myopathic EDS	mEDS	AD or AR	*COL12A1*	Type XII collagen
13	Periodontal EDS	pEDS	AD	*C1R* *C1S*	C1r C1s

IP, inheritance pattern; AD, autosomal dominant; AR, autosomal recessive, NMD, nonsense-mediated mRNA decay.

Diagnostic criteria for Ehlers-Danlos syndrome

This is a condition that is difficult to diagnose and is often confused with other diseases (6) due to its complex and nonspecific symptoms. Despite constant updates to diagnostic guidelines, it remains widely underdiagnosed, directly compromising the patient's life quality (1).

General symptoms of cEDS and hEDS

The genetic abnormality directly affects collagen synthesis, causing a range of symptoms that extend from abnormal elasticity of the skin and ligaments to neurological and psychiatric problems.

Both subtypes present similar symptoms, such as joint hypermobility, skin hyperelasticity, atrophic scars, stretch marks, frequent dislocations or subluxations, muscle and vascular fragility

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(spontaneous bruising, edema), as well as intestinal and urinary manifestations (particularly bladder problems).

The diagnosis of cEDS is based on the patient's medical history and physical examination (11), by process of elimination (1). Diagnosis is complex due to the wide range of symptoms, and other conditions that cause similar symptoms must be ruled out. Differentiation between the two types is not possible in the absence of genetic testing, given the overlap in clinical presentation. When no genetic marker is identified, the hypermobile type is the presumptive diagnosis.

Classical Ehlers-Danlos Syndrome (cEDS)

In the classical form (cEDS) mutations in the COL5A1, COL5A2, and COL1A1 genes affect type V and I collagen. The criteria used are basically the same as for hEDS; the Beighton scale should be used at all ages as one of the diagnostic criteria. However, genetic testing can determine which type of collagen is affected; in cEDS, it is type V collagen.

> Previous question marks over genetic heterogeneity have been largely surpassed by evidence that abnormalities in type V collagen are the cause. Advances in molecular testing have made it possible to identify the causative mutation in the majority of patients. (12, p. 27–39)

Collagen V is found in the endothelium, which explains the various symptoms that may appear unrelated, particularly those affecting the intestines and bladder. The vascular fragility in these patients can make the peripheral venous network very fragile, making procedures such as venipuncture difficult.

Hypermobile Ehlers-Danlos Syndrome (hEDS)

A questionnaire is available on the Ehlers-Danlos Society website (11), which includes diagnostic criteria for Ehlers-Danlos Hypermobile Syndrome. These criteria consist of three items: the Beighton scale, questions regarding skin flexibility assessment, atrophic scarring, cardiovascular evaluation, family history, musculoskeletal pain, joint instability, and exclusion of other diseases.

hEDS also presents with complications and symptoms of neuropathy, just as in cEDS and other subtypes of EDS (13).

Comorbidities - Relationship between Ehlers-Danlos Syndrome and other conditions

According to the Ehlers-Danlos Society website (11), comorbidities may include motor problems, dysautonomia, impaired proprioception, chronic fatigue syndrome, sleep disturbances, mood swings, and other symptoms described below:

> The diagnostic criteria, additional mucocutaneous, osteoarticular, musculoskeletal, cardiovascular, gastrointestinal, uro-gynecological, neuropsychiatric, and atopic issues, and facial/ocular features were ascertained, and feature rates compared by sex and age. (14, p. 197)

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Chronic pain is the most common comorbidity in EDS due to constant muscle injuries (15). Many patients are initially diagnosed with fibromyalgia. As Pimiento and Vergara-Garcia point out (16, pp. 1–13, 2024), “Diagnosing EDS and fibromyalgia can be challenging in medical practice as clinical manifestations can overlap, and they may even coexist in the same patient.”. Pain, which is processed in the same brain regions as emotions, is associated with mood swings. “It is a complex phenomenon resulting from sensory stimuli or neurological damage, and it can be influenced by a person’s memories, expectations, and emotions.”(17) In addition to chronic pain, chronic fatigue syndrome is associated with non-restorative sleep in patients with Ehlers-Danlos syndrome (18). Cazzato et al. (13, pp. 155 - 159) point out that small-fiber neuropathies are common, causing hyperalgesia, numbness, and “sock-shaped” pain, which complicates the differential diagnosis.

EDS/hEDS is significantly associated with ADHD (p=0.02) and ASD (19). Children with ADHD and hEDS showed a higher prevalence of associated symptoms (fatigue, sleep disturbances, urinary symptoms). ASD was identified in 6% of cases, with 92% of these individuals exhibiting sleep disturbances (19).

Marfan syndrome is also associated with EDS and can frequently be misdiagnosed.

A common finding associated with the COL5A1 gene is musculoskeletal injuries characterized by slow recovery (15), particularly injuries to the anterior cruciate ligament of the knee (20).

EDS’s underreporting

Although the prevalence of cEDS is 1 to 9 per 100,000 individuals (7) and is considered rare, some authors believe it is underreported due to the difficulty in diagnosing the syndrome, and the prevalence may actually be as high as 1 in every 600 to 900 people (4). It is often misdiagnosed as other diseases, because the symptoms are vague and nonspecific; it is described as “a rare genetic disorder that is constantly evolving and remains significantly underdiagnosed, with a direct impact on the patient’s life quality” (1)

EDS’s pathophysiology

Defective collagen synthesis is considered to cause tissue fragility, leading to connective tissue damage and delayed healing. Therefore, understanding the structural organization of collagen is essential for the pathophysiological elucidation of EDS.

Structure of collagen

Collagen forms a triple helix composed of glycine, proline, and hydroxyproline (21). There are about 30 types, with type I being the most common, classified as: long fibrils (I, II, III, V, XI), associated fibrils (IX, XII, XIV), network fibrils (IV), and anchoring fibrils (VII) (22).

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Lompa (23, pp. 20–21) reports on a comparison of muscle tissue biopsies between athletes with and without hypermobility, which the study refers to as Hypermobility Syndrome (HMS): “The underlying collagen defect in HMS.” The study continues:

> An increase in the elastic tissue of the lamina propria (chorion) has been described by several authors, and morphological abnormalities of the elastic fibers have been documented. Pautrier found that the elastic fibers of the corium were normal, while Brown and Stock believed they were diminished. Jansen, in 1955, demonstrated with excellent illustrations that in normal skin there is a system of interwoven, robust, and well-aligned collagen fibers. In hyperelastic skin (EDS), the most evident structural change is that the collagen fibers appear to have been insufficiently bound. Electron microscopy showed that the morphological aspects of collagen and elastin were normal. (23, p. 20 - 21)

Vitamin c and collagen

Vitamin C stabilizes the structure of collagen through lysine and proline hydroxylases (24), playing an essential role in its synthesis, with particular relevance to EDS (9). Reduced levels explain the “insufficiently bound” collagen fibers observed by Lompa (23, pp. 20–21), compromising angiogenesis and wound healing, the latter being a diagnostic criterion for hEDS.

> Vitamin C is an essential cofactor for proline and lysine hydroxylases involved in collagen synthesis. Vitamin C deficiency reduces collagen deposition during wound healing and compromises angiogenesis, leading to the development of hemorrhages and decreased scar strength. However, these harmful effects of vitamin C deficiency on wound healing do not actually manifest clinically until much later, after 180 days of deprivation, and there is no clear evidence that vitamin C supplementation in amounts exceeding daily requirements accelerates wound healing. (10, p. 1-10)

Ehlers-Danlos Hypermobile without an identified gene

hEDS without a genetic cause has been linked to certain genes responsible for low levels of vitamin C (9)

> Germline DNA was analyzed by whole genome sequencing (WGS) analysis and an in silico panel of 170 genes associated with bleeding and generalized HM was examined. Additionally, homozygous polymorphism in vitamin C genes (GULOP, SLC23A1, SLC23A2, SVCT1, HP, GST and SOD2) known to cause reduced vitamin C levels. (9, p. 1 - 2).

And concludes that patients with hypermobility have a higher ISTH-BAT score (Bleeding Assessment Tool - a standardized questionnaire for assessing bleeding symptoms) compared to individuals with a negative Beighton score. However, they suggest that more studies are needed on this genetic relationship.

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Treatment

Ehlers-Danlos Syndrome (EDS) has various non-specific symptoms resulting from a defect in collagen synthesis, requiring a multidisciplinary approach to treatment (1). According to Bravo (25, 1493–1502), management includes: preventive measures involving exercise; treatment of acute joint injuries with anti-inflammatory drugs, analgesics, and ultrasound; chronic treatment with a rheumatologist and pain management; physical therapy; medications; control of dysautonomia through hydration and drugs; as well as cardiological and vascular follow-up for vascular fragility with a risk of aneurysms in COL5A1 mutations, according to Bowen (12, pp. 27–39), and musculoskeletal and autonomic manifestations. A multidisciplinary approach typically prioritizes symptom management and the prevention of complications, such as falls and tissue injuries, adapting to the specific needs of each patient, and emphasizing the necessity of a multidisciplinary team for comprehensive care.

Given the vascular fragility of individuals with EDS (9)(23), nurses need to pay closer attention to venipuncture in contexts where it is necessary, as part of multidisciplinary care.

Muscle strengthening and orthotics

Because of musculoskeletal problems, vascular issues, and chronic pain, it is recommended that patients engage in regular physical exercise that is adapted to their functional limitations (5). These exercises should preferably be low-impact, avoiding activities that cause joint trauma, advising the patient on contact sports, and emphasizing the importance of muscle and tendon strengthening, in consultation with a physical therapist (1). Orthoses, prostheses, and compression stockings may be used for joint stabilization in various parts of the body and to aid venous return in the lower limbs (1).

Pain control

Ehlers-Danlos patients routinely suffer from chronic pain (16), requiring pharmacological and non-pharmacological treatments prescribed by a pain specialist. Non-pharmacological treatments include exercise, heat therapy, and orthotics.

> The most effective treatments reported were heating pads and braces. Cold showers and CrossFit were considered the least effective. CrossFit and horse riding were the treatments most reported as being harmful.[...] Patients reported a high number of treatments and strategies used to manage and self-manage chronic pain, albeit many with minimal analgesic benefit (26, p. 1).

Pharmacological treatment includes analgesics, muscle relaxants, SSRIs, tricyclic antidepressants, SNRIs, and gabapentinoids for pain management, as well as nutritional supplementation (24).

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Psychological and psychiatric treatment

Chronic pain causes psychological disturbances, requiring professional intervention; psychiatric and psychological treatment may also be necessary.(27)

Nutritional supplementation

Nutritional supplementation is often overlooked in the treatment of EDS (8). Patients with cEDS experience slow muscle recovery and post-exercise pain (14); protein supplementation may offer benefits in management of the syndrome's musculoskeletal clinical manifestations.

> Protein, especially branched-chain amino acids (BCAAs), is a key component of muscle repair. It not only facilitates recovery after exercise, but also modulates the immune system and hormonal regulation, vital functions that are often compromised when training intensively. (28)

Arginine may also support muscle tissue recovery and functional improvement (29).

Vitamin C supplementation may improve connective tissue health and wound healing. “Regular intake of folic acid, vitamin C, and vitamin D may be helpful” (30).

> We recommend to these patients to take 0.4 to 1 mg of folic acid (FA) daily on a long-term basis, as studies show that FA deficiency alters collagen chains, leading to tissue weakness. Magnesium is helpful for cramps, and in cases of capillary fragility—as well as to prevent contusions, vitamin C or a multivitamin should be prescribed. It is important to detect and treat osteoarthritis early. The use of glucosamine alone or with chondroitin sulfate to prevent osteoarthritis is suggested by some and appears to be helpful, but further studies are needed to confirm this. Treatment of the syndrome should begin as soon as possible in the usual manner (25, p. 1495).

There is some evidence that vitamin C supplementation may help improve wound healing:

> Wound healing was more effective in the groups treated with vitamin C compared to the group that did not receive vitamin supplementation. There was no significant difference in wound healing between the groups that received oral or subcutaneous vitamin C (31, p. 1).

Collagen supplementation may also aid in wound healing and is effective in promoting tissue repair (27). The interaction between collagen and vitamin C accelerates tissue repair, increasing the strength and capacity of connective tissue.

> The bioavailability and efficacy of collagen are enhanced when co-administered with vitamin C, an essential cofactor for collagen synthesis. Vitamin C participates in hydroxylation reactions, a crucial step in the maturation and stabilization of collagen fibers. This nutritional synergy not only accelerates the tissue repair process but also optimizes the strength and functionality of connective tissues.(...)
> (…)The synergy between collagen and vitamin C illustrates a combined strategy for strengthening connective tissues, supporting athletes’ endurance, and preventing injuries (29, p. 129-32).

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The nutritional therapies listed above hold great potential when used as an adjunct to symptomatic treatment, offering the possibility of an overall improvement in the health of patients with the syndrome and tissue repair.

METHODOLOGY

This study is a scientific literature review with a qualitative and descriptive approach (traditional narrative review), aimed at compiling, examining, and summarizing current scientific knowledge on the topic, including the evaluation of previously published studies in English, Spanish, or Portuguese found in indexed databases, DECS (Health Sciences Descriptors), Google Scholar, Orphanet, and articles available on the Ehlers-Danlos Society website (11). Articles were selected based on specific criteria to ensure the relevance and quality of the data. This is not a systematic review with a rigid protocol, but rather a narrative literature review using defined keywords.

The research strategy consisted of a comprehensive and intersectional thematic search, using umbrella terms and cross-referencing them with intervention descriptors, genetic markers, and comorbidities, with the aim of gathering as much evidence as possible from the scientific literature. Thirty one (31) studies were selected, including clinical trials, cohort studies, qualitative research, master's thesis and reviews. The analysis covered publications from 1996 to 2024, identifying the main complications of EDS, clinical manifestations, articles linking genetics and pathophysiology involved in hEDS and hypermobility, tissue damage caused by collagen-related problems, based on a search for articles linking vitamin C with hypermobility and/or EDS, and the role of vitamin C and protein supplementation in tissue repair. The articles were categorized into four main thematic axes: (a) pathophysiology and genetic basis of classical EDS (cEDS) and hypermobile EDS (hEDS); (b) clinical manifestations and associated comorbidities; (c) multidisciplinary therapeutic approaches; and (d) the role of nutritional supplementation, with an emphasis on vitamin C, as well as articles on treatments targeting the improvement of collagen I, II, III, and V structure and treatments related to muscle injury (14), according to the relevance of the data in treatments corresponding to the guiding question.

The methodological quality of the studies was varied and heterogeneous, due to the lack of specific studies. One study was found that examined the relationship between vitamin C levels and hypermobility. It is suggested that vitamin C may be a promising option for treatment, but the absence of uniformity in study protocols and the necessity for further research limit the conclusions of this review.

A comprehensive combination of terms in Portuguese, Spanish, and English was employed, including controlled descriptors and free-text words, implicit Boolean operators (represented by the "+" sign), and synonyms. The search was conducted using the following keywords: Ehlers-Danlos syndrome; Ehlers-Danlos; Ehlers-Danlos + vitamin C; hypermobility + vitamin C; SLC23A1 + hypermobility; COL5A1; COL5A1 + Ehlers-Danlos; SLC23A1 + Ehlers-Danlos; rheumatology; genetics; hypermobility + treatment;

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Ehlers-Danlos + therapy; collagen; collagen + vitamin C; collagen V; collagen structure; Ehlers-Danlos ADHD; Ehlers-Danlos + fibromyalgia; chronic pain + hypermobility; vitamin C + collagen; muscle injury; supplementation EDS + vitamin C.

Exclusion criteria were implemented to improve the selection of articles. Articles that were not relevant to the topic at hand or to topics related to the objectives of the review were excluded. Articles on veterinary medicine and those specific to other subtypes of EDS unrelated to the subtypes listed, or irrelevant to EDSc and EDSh, were also excluded, as were articles containing more recent updates on the same subject. Articles whose content was not relevant to the objectives of this review were also excluded. Exclusion was based on failure to meet the described specificity criteria.

RESULTS AND DISCUSSION

The findings of this review show that cEDS is associated with well-established mutations in the COL5A1 and COL5A2 genes and, more rarely, in the COL1A1 gene, resulting in alterations in the synthesis and structure of type V and I collagen (12). Although there is no recognized genetic marker for hEDS, a very similar range of symptoms can be observed in both subtypes. This clinical convergence supports the hypothesis that the final pathophysiological pathways, centered on collagen integrity and stability, may be shared.

The studies reviewed indicate that EDS is a multisystemic syndrome, whose manifestations extend beyond the musculoskeletal system, and systemic complications emerge, becoming crucial determinants of quality of life. Symptomatic overlap with fibromyalgia is also frequently reported, which can lead to diagnostic delays and inappropriate therapeutic approaches. Chronic pain stands out as the most prevalent and disabling comorbidity (14) (16). Recurrent muscle damage, resulting from joint instability and connective tissue fragility, establishes a vicious cycle of injury, pain, and physical deconditioning, as small-fiber neuropathies, described by Cazzato et al. (13, pp. 155–159), emerge as a relevant finding in the pathophysiology of pain in EDS. Hyperalgesia, paresthesias, and pain with a “stocking” or “glove” distribution suggest nerve fiber involvement, contributing to the chronicity of symptoms and resistance to conventional analgesics.

Dysautonomia, chronic fatigue, orthostatic intolerance, and sleep disturbances are highly prevalent in EDS. Guilleminault et al. (18, pp. 1503–1511) documented a significant association between EDS and sleep disorders, as well as neuropsychiatric manifestations. Kindgren et al. (19, pp. 379–388) demonstrated a significant association between hEDS and Attention-Deficit/Hyperactivity Disorder (ADHD) ($p=0.02$), as well as an increased prevalence of Autism Spectrum Disorder (ASD), reaching 6% in the studied population, of whom 92% exhibited sleep disturbances. These findings suggest common pathophysiological mechanisms, possibly related to alterations in the extracellular matrix of the central nervous system or to shared epigenetic mechanisms.

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Vitamin C deficiency compromises collagen stability, reduces tissue tensile strength, and impairs angiogenesis (10). These mechanisms may explain the capillary fragility, spontaneous bleeding, and impaired wound healing observed in cEDS and hEDS. Furthermore, these levels may explain the “insufficiently bound” collagen fibers observed by Lompa (23, pp. 20–21), which compromises angiogenesis, directly affecting wound healing.

The single study linking hypermobility to vitamin C deficiency has investigated polymorphisms in genes related to vitamin C metabolism (GULOP, SLC23A1, SLC23A2, SVCT1, HP, GST, and SOD2) in patients with generalized hypermobility and bleeding of undetermined cause. The authors observed a correlation between high scores on the ISTH-BAT scale (bleeding assessment) and joint hypermobility, suggesting that genetic variants that reduce circulating vitamin C levels may contribute to the hypermobile phenotype. However, this single study is not sufficient to make conclusive statements.

Future research should prioritize longitudinal studies evaluating different vitamin C supplementation regimens, in addition to genomic studies aimed at identifying predictive markers of therapeutic response, since vitamin C, as an essential cofactor for hydroxylases, enhances the bioavailability and efficacy of supplemental collagen, accelerating tissue repair and optimizing the strength and functionality of connective tissues. While experimental studies demonstrate accelerated wound healing with supplementation (30), extrapolating these findings to clinical practice faces methodological limitations. There is no consensus among the included studies regarding optimal doses, routes of administration, or duration of treatment. Interindividual variability in the absorption and metabolism of vitamin C, determined by genetic polymorphisms, adds to the complexity of standardizing protocols. Pereira et al. (28, p. e67513-e67513) highlight the role of branched-chain amino acids (BCAAs) in muscle repair, immune modulation, and hormonal regulation. Arginine, in addition, may contribute to functional improvement in muscle tissue (29), although specific studies on SED are needed. Bravo (25, 30) proposes a supplementation regimen including folic acid (0.4 to 1 mg/day), vitamin C, vitamin D, and magnesium for cramps. Folic acid is justified by studies demonstrating that its deficiency alters collagen chains, leading to tissue weakness.

From the perspective of impaired angiogenesis (23), it is worth highlighting the precautions that nurses should take regarding venipuncture in these patients; although there are no specific studies linking the vascular fragility of patients with EDS to venipuncture and venous access devices, the evidence suggests that these patients may experience problems with venipuncture.

The main limitation identified in this review is the scarcity of controlled studies on specific therapeutic interventions for cEDS and hEDS. The standardization of clinical protocols and the inclusion of integrative approaches, such as physical therapy and personalized nutritional counseling, are also essential for improving patients’ life quality. Although this review points to promising avenues, optimizing the management of EDS still depends on advances in translational research and the implementation of evidence-based therapeutic strategies.

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CONCLUSION

This literature review aimed to provide a comprehensive examination of the classical (cEDS) and hypermobile (hEDS) subtypes of Ehlers-Danlos syndrome, assessing their genetic and pathophysiological basis as well as current therapeutic options, with a particular focus on the role of vitamin C and nutritional supplementation. Although cEDS and hEDS have distinct genetic etiologies (or as yet unidentified ones, in the case of hEDS), they share common pathophysiological pathways related to connective tissue integrity.

It has become evident that the most significant symptoms of EDS are related to tissue damage caused by structural changes in collagen, which adversely affects patients' quality of life and cannot be considered a condition limited to the musculoskeletal system, but rather constitutes a multisystemic syndrome that also requires an extensive and integrated diagnostic and therapeutic approach, which underscores the need to move beyond the current paradigm of strictly symptomatic interventions.

Multidisciplinary treatment, including muscle strengthening, orthotics, pharmacological pain management, and psychological support, is the current standard of care. Muscle strengthening is essential for joint stabilization and non-pharmacological pain management, though pharmacological interventions, if necessary, should not be ignored. Interdisciplinary care has proven to be essential.

The possible relationship between hEDS (which still lacks a defined genetic marker) and genes that regulate vitamin C metabolism: the findings of this review, although limited to a single study, offer a biologically plausible hypothesis, given the fundamental role of ascorbic acid as a cofactor for the hydroxylases that stabilize collagen fibers. Enlightening the potential interface between vitamin C and the phenotypic expression of the syndrome, it will be possible to formulate new research hypotheses and to establish more rational and personalized therapeutic strategies capable of overcoming the current fragmentation.

This research scope was limited, both by the lack of comprehensive reviews and by the scarcity of specific studies on the topic. The field of EDS treatment remains highly fragmented. Large-scale genomic studies, including whole-exome sequencing and analysis of polymorphisms in genes involved in vitamin C metabolism, may shed light on the molecular basis of EDS and identify subgroups with a potential response to supplementation. There is great potential in research on therapeutic approaches to improve wound healing and tissue repair, as well as overall improvement in connective tissue health.

Future research perspectives should prioritize randomized clinical trials evaluating different vitamin C supplementation regimens, with standardized outcomes (wound healing, pain, quality of life); longitudinal, controlled clinical trials evaluating the efficacy of different supplementation protocols (doses, routes, and nutrient combinations) in improving symptoms, quality of life, and tissue repair in these patients; and the development of standardized clinical guidelines that integrate nutritional care into a

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multidisciplinary approach; validation of physical rehabilitation protocols adapted to the specific characteristics of EDS; investigation of combined nutritional interventions (vitamin C, collagen, amino acids). Optimizing the management of EDS depends on advances in translational research, integrating genetic, biochemical, and clinical knowledge to develop evidence-based therapeutic strategies personalized to the individual patients' needs. In summary, this review systematizes current knowledge on cEDS and hEDS, emphasizing the importance of a clinical approach that integrates genetics, biochemistry, and the therapeutic strategies used in the treatment of EDS. The professionals most likely to come into contact with these patients include: physicians practicing in so-called “pain treatment centers,” rheumatologists, physiatrists, physical therapists, and physical education teachers. This does not exclude nurses, who often have direct contact with patients in the context of multidisciplinary treatments. These professionals need to be alert to the differential diagnosis for this condition.

REFERENCES

1 Misukami DR, Marques DV, da Silva MPF, Ferreira BA, de Oliveira SNP, Loinaz VG, et al. Síndrome de Ehlers-Danlos: uma abordagem diagnóstica, evolução clínica e revisão. Braz. J. Hea. Rev. [Internet]. 2023 Sep. 18; 6(5):21685-97. Available from: https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/view/63144

2 Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):8-26. doi: 10.1002/ajmg.c.31552. PMID: 28306229.

3 Wells RHC, et al. CID-10: classificação estatística internacional de doenças e problemas relacionados à saúde. São Paulo: EDUSP; 2011.

4 Ehlers-Danlos Society. Are the Ehlers-Danlos syndromes and hypermobility spectrum disorders rare or common? [Internet]. 2024. Disponível em: https://www.ehlers-danlos.com/is-eds-rare-or-common/

5 Stephanny E, Ribas F, Ganassini Quintanilha H, Ril Izd Sin, de F, Goulart Japiassu L, Nunes Carvalho M, Dias L, Carneiro Yamashita N, Gonzaga W, Alvar Garcia A, de I, Beatriz A, Antunes D, Filipe J, Pinheiro J, Souza A, Queirós Rodrigues L, Cardoso F, Lucas. Síndrome de Ehlers-Danlos. Braz J Health Rev [Internet]. 2022; 5(5):18583-91. Disponível em: https://doi.org/10.34119/bjhrv5n5-065.

6 Hamonet C, Frédy D, Marié-Tanay C, Ducret L, Bahloul H, Guinchat V, et al. Ehlers-Danlos syndrome (EDS) a diagnostic trap for the neurologist, an iatrogenic risk for the patient. EC Neurol. 2017;7(2):46-53.

7 ORPHANET. Orphanet: Síndrome Ehlers-Danlos clássico [Internet]. Orpha.net. 2023. Available from: https://www.orpha.net/pt/disease/detail/287

8 Quispe Pari GD. Síndrome de Ehlers-Danlos (SED). Rev Act Clin Med [Internet]. 2014; 45. Available from: http://revistasbolivianas.ciencia.bo/pdf/raci/v45/v45a02.pdf

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SCIENTIFIC JOURNAL - RECIMA21 ISSN 2675-6218

9 Halla Fridriksdottir, Rasmussen AØ, Lykkesfeldt J, Rossing M, Leinoe EB. Reduced vitamin C levels in patients with bleeding of unknown cause and generalized joint hypermobility. Blood. 2023 Nov 2;142(Suppl 1):25.

10 Senet P. Fisiología de la cicatrización cutánea. EMC-Dermatol. 2008;42(1):1-10.

11 The Ehlers Danlos Society. The Ehlers Danlos Society [Internet]. 2016. Available from: https://www.ehlers-danlos.com/

12 Bowen JM, Sobey GJ, Burrows NP, Colombi M, Lavallee ME, Malfait F, Francomano CA. Ehlers-Danlos syndrome, classical type. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):27-39. doi: 10.1002/ajmg.c.31548. Epub 2017 Feb 13. PMID: 28192633.

13 Cazzato D, Castori M, Lombardi R, Caravello F, Bella ED, Petrucci A, Grammatico P, Dordoni C, Colombi M, Lauria G. Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. Neurology. 2016 Jul 12;87(2):155-9. doi: 10.1212/WNL.0000000000002847. Epub 2016 Jun 15. PMID: 27306637; PMCID: PMC4940063.

14 Ritelli M, Venturini M, Cinquina V, Chiarelli N, Colombi M. Multisystemic manifestations in a cohort of 75 classical Ehlers-Danlos syndrome patients: natural history and nosological perspectives. Orphanet J Rare Dis. 2020;15(1):197.

15 Baumert P; G-REX Consortium; Stewart CE, Lake MJ, Drust B, Erskine RM. Variations of collagen-encoding genes are associated with exercise-induced muscle damage. Physiol Genomics. 2018 Sep 1;50(9):691-693. doi: 10.1152/physiolgenomics.00145.2017. Epub 2018. PMID: 29799806; PMCID: PMC6172608.

16 Pimiento DCN, Vergara-Garcia D. Ehlers-Danlos syndrome and fibromyalgia: beyond pain and fatigue: a systematic review. Rev Salud Bosque. 2024;14(1):1-13.

17 da Silva JA, Ribeiro-Filho NP. A dor como um problema psicofísico. Revista Dor. 2011 Jun;12(2):138–51.

18 Guilleminault C, Primeau M, Chiu HY, Yuen KM, Leger D, Metlaine A. Sleep-disordered breathing in Ehlers-Danlos syndrome: a genetic model of OSA. Chest. 2013 Nov;144(5):1503-11.

19 Kindgren E, Quiñones Perez A, Knez R. Prevalence of ADHD and Autism Spectrum Disorder in Children with Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome: A Retrospective Study. Neuropsychiatric Disease and Treatment. 2021 Feb;Volume 17(2021):379–88.

20 Calò CM, Massidda M, Sorge R, Tiloca A, Monteleone G. Gene COL5A1 e o risco de lesões do LCA no esporte de equipe: um relatório preliminar. Rev Bras Ortop. 2024 Apr 22;59(4):e584-9.

21 Patino MG, Neiders ME, Andreana S, Noble B, Cohen RE. Collagen: an overview. Implant Dent. 2002;11(3):280-5.

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SCIENTIFIC JOURNAL - RECIMA21 ISSN 2675-6218

22 Santos VS. Colágeno [Internet]. Brasil Escola. 2020 fev 3. Disponível em: https://brasilescola.uol.com.br/biologia/colageno.htm

23 Lompa PA. Incidência de lesões esportivas em atletas com e sem síndrome de hipermobilidade articular familiar [dissertação]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 1996.

24 Savini I, Rossi A, Duranti G, Avigliano L, Catani MV, Melino G. Characterization of keratinocyte differentiation induced by ascorbic acid: protein kinase C involvement and vitamin C homeostasis. J Invest Dermatol. 2002;118(2):372-9.

25 Bravo JF. Síndrome de Ehlers-Danlos (SED) con especial énfasis en el síndrome de hiperlaxitud articular (SHA). Rev Med Chil. 2009;137:1493-502.

26 Eduarda M. Relief of chronic musculoskeletal pain in patients diagnosed with Ehlers-Danlos Syndrome (EDS): a questionnaire-based study. Handlenet [Internet]. 2020 Apr 29; Available from: https://hdl.handle.net/10216/128710

27 Morales CRB, Silva AR, Silva GR. Aspectos psiquiátricos na Fibromialgia: uma revisão de literatura. Braz J Health Rev. 2023;6(4):16331-4.

28 Pereira DM, dos Santos VT, Vilela MM, de Oliveira TM, Oliveira DC, Junior JKK. Contribuição da nutrição para a prevenção e recuperação da Síndrome do Overtraining em atletas. Braz. J. Hea. Rev. [Internet]. 2024 Feb. 23 [cited 2026 Mar. 11];7(1):e67513. Available from: https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/view/67513

29 Angeli G, Barros TLD, Barros DFLD, Lima M. Investigation of the effects of oral supplementation of arginine in the increase of muscular strength and mass. Rev Bras Med Esporte. 2007;13:129-32.

30 Bravo JF. Síndrome de Ehlers-Danlos Clásico o Ehlers-Danlos tipo I-II. Rev Chil Reumatol. 2016;32(4):123-30.

31 Da Silva LCK, et al. Efeito da suplementação de vitamina C no tempo de cicatrização em procedimentos neurocirúrgicos. Arq Bras Neurocir. 2018;37(S 01):A1314.

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