CORRELATION OF HYPERMOBILE EHLERS-DANLOS SYNDROME (EDS) AND THE JOINT DAMAGE ON DAILY LIFE OF AFFECTED PATIENTS: A BIBLIOGRAPHIC REVIEW

ABSTRACT

Ehlers-Danlos Syndrome, known by the acronym EDS, is a genetic pathology that affects the synthesis of collagen, the main constituent protein connective tissue in the human body. Over the centuries, this pathology has been described several times, having its beginning in the 17th century with a superficial explanation that did not specifically detail the symptoms seen today for the disease. Only at the beginning of the 20th century did doctors Edward Ehlers and Alexandre Danlos define the primary postulations regarding SED as understood today. From of these definitions, in 2017 the parameters and types

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of that Syndrome were discussed that exist in the world, namely: vascular, astrochalasis, dermatoparaxis, fragile cornea syndrome, hypermobile etc. A protein affected by EDS, collagen, presents a biosynthesis signaled by polyribosomes of the REG where it begins as pre-procollagen and ends in formation of fibrilas in the extracellular environment, when it comes to fibrillar collagens, composing the tension-resistant structure that forms tendons and joints, for example. In ED Syndrome, the mutation affects the biosynthesis of specific types of collagens, especially the fibril-forming ones (I, II, III, V and XI), affecting the formation of important components of the human body and causing problems in the structure of the body’s joints, in a Brazilian context, mostly the glenohumeral joint. An Ehlers-Danlos syndrome presents as its main symptoms pain, fatigue, dystonia, dysautonomia, joint hypermobility and skin hyperextensibility and their signs are noticeable from birth. After noticing these signs, you should carry out a clinical analysis and later a genetic one to define ways of treatment and rehabilitation for patients affected by EDS, being indicated mainly physiotherapy and social support treatments.

Keywords: Ehlers-Danlos Syndrome; joints; rheumatology.

RESUMO
A Síndrome de Ehlers-Danlos, conhecida pela sigla SED, é uma patologia genética que afeta a síntese de colágeno, principal proteína constituinte do tecido conjuntivo do corpo humano. Ao longo dos séculos, esta patologia foi descrita diversas vezes, tendo o seu início no século XVII com uma explicação superficial que não detalhava especificamente os sintomas hoje observados para a doença. Somente no início do século XX os médicos Edward Ehlers e Alexandre Danlos definiram as principais postulações sobre o SED tal como é entendido hoje. A partir dessas definições, em 2017 foram discutidos os parâmetros e tipos dessa Síndrome que existem no mundo, a saber: vascular, astrocálice, dermatoparaxia, síndrome da córnea frágil, hipermóvel etc. pelos polirribossomos do REG onde começa como pré-procolágeno e termina na formação de fibrilas no meio extracelular, quando se trata de colágenos fibrilares, compondo a estrutura resistente à tensão que forma tendões e articulações, por exemplo. Na Síndrome de Ehlers-Danlos a mutação afeta a biossíntese de tipos específicos de colágenos, principalmente os formadores de fibrilas (I, II, III, V e XI), afetando a formação de componentes importantes do corpo humano e causando problemas na estrutura de as articulações do corpo, no contexto brasileiro, principalmente a articulação glenoumeral. A síndrome de Ehlers-Danlos apresenta como principais sintomas dor, fadiga, distonia, falta de autonomia, hipermobibilidade articular e hiperextensibilidade da pele e seus sinais são perceptíveis desde o nascimento. Após perceber esses sinais, deve-se realizar uma análise clínica e posteriormente genética para definir formas de tratamento e reabilitação dos pacientes acometidos pela SED, sendo indicados principalmente tratamentos de fisioterapia e apoio social.

Palavras-chave: Síndrome de Ehlers-Danlos; articulações; reumatologia.

RESUMEN
El síndrome de Ehlers-Danlos, conocido por sus siglas SED, es una patología genética que afecta la síntesis de colágeno, la principal proteína constituyente del tejido conjuntivo del cuerpo humano. A lo largo de los siglos, esta enfermedad ha sido descrita en varias ocasiones, comenzando en el siglo XVII con una explicación superficial que no detallaba específicamente los síntomas observados hoy en día para la enfermedad. Solo a principios del siglo XX, los médicos Edward Ehlers y Alexandre Danlos definieron las principales postulaciones sobre el SED tal como se entiende hoy. A partir de estas definiciones, en 2017 se discutieron los parámetros y tipos de este síndrome que existen...
en el mundo, a saber: vascular, astrocálase, dermatoparaxia, síndrome de la córnea frágil, hipermovilidad, etc. La mutación en el Síndrome de Ehlers-Danlos afecta la biosíntesis de tipos específicos de colágeno, principalmente los formadores de fibrillas (I, II, III, V y XI), afectando la formación de componentes importantes del cuerpo humano y causando problemas en la estructura de las articulaciones del cuerpo, principalmente la articulación glenohumeral en el contexto brasileño. El síndrome de Ehlers-Danlos presenta como principales síntomas dolor, fatiga, distonía, falta de autonomía, hipermovilidad articular e hiperextensibilidad de la piel, y sus signos son perceptibles desde el nacimiento. Después de notar estos signos, se debe realizar un análisis clínico y posteriormente genético para definir formas de tratamiento y rehabilitación de los pacientes afectados por el SED, siendo los tratamientos de fisioterapia y apoyo social los más indicados.

**Palabras clave:** Síndrome de Ehlers-Danlos; articulaciones; reumatología.

### 1. Introduction

The diagnosis of rare diseases, since the beginning of humanity's medical knowledge, has been extremely difficult mainly due to the lack of knowledge about the diseases analyzed. In a macroscopic analysis, rare diseases are those that are infrequent in a population and have complex management approaches and often lead to the death of the affected patient (Auvin et al., 2018).

Therefore, Ehlers-Danlos Syndrome, popularly known as EDS, is a rare pathology caused by mutations in genes encoding collagen in the human body, causing changes in the structures that use this protein in their composition, such as the joints and lining epithelia of the entire organism, generally affects the connective tissue. As it is a genetic disease, the syndrome has subtypes according to the affected gene, with 13 subtypes currently present (Espósito et al., 2016). EDS presents an eminently clinical and difficult to definitive diagnosis with a strong link to heredity, presenting symptoms shared between the various subtypes of the pathology (Chatovski, 2021).

In historiography, Ehlers-Danlos Syndrome was described for the first time in the 17th century by the Dutch surgeon Job Janszoon van Meek'ren, where a 23-year-old Spanish patient was analyzed, however he did not present all the symptoms currently described for EDS (Espósito et al., 2016). Over the centuries, other doctors described the disease, gradually adding the symptoms that we see today in the diagnosis of the syndrome.

However, it was only at the beginning of the 20th century that the EDS
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seen today took shape and name when the Danish dermatologist Edward Ehlers, in 1901, and the French doctor Alexandre Danlos, in 1908, analyzed the symptoms and consequences associated with a lack of collagen in the human body in their patients, such as the propensity to hemorrhage and the anomalous growth of scars (Espósito et al., 2016) (Miller, 2018).

Classic EDS comprises most of all cases and its statistics are estimated at 1:20,000 in the population. Joint hypermobility is one of the classic manifestations of EDS in articles published in the literature about the disease. This signal can be calculated using the Brighton scale, a parameter used to determine the degree of hypermobility (Bem-Haja et al., 2016).

Furthermore, it is important to highlight that in Brazil, PL 4817/19, a bill that aims to create the “National Policy for Comprehensive Care for People with Ehlers-Danlos Syndrome and Hypermobility Syndrome”, aiming to improve the conditions of access to health of people affected by this syndrome.

In general, hypermobile EDS causes massive damage to joints throughout the body and is not limited to specific locations. However, some areas, such as the glenohumeral region, are more susceptible to problems associated with the fragility of collagen fibers due to the syndrome, considering that much of the individual's life they will use this joint as support to carry out some activity, in addition to it will be the basis for movement of the upper limbs.

2. Material and Methods

This is review based on the analysis of technical-scientific knowledge obtained through online scientific dissemination platforms (PubMed, Lilacs and Scielo) and highly relevant literature, with chronological cut between 2007 and 2021. Furthermore, the inclusion criteria include being in the chronological window and reporting Ehlers-Danlos Syndrome in some way, with priority given to cases of hypermobility. Exclusion means not meeting the two subsequent criteria simultaneously. To establish the keywords, DeCS was used with its variations in Portuguese, English and Spanish.
3. Results

From this point of view, patients affected by this genetic syndrome of multisystem involvement have several difficulties and limitations in their daily lives, in view of the physiological implications that EDS generates on their bodies, such as: disabling the transport of heavy objects in situations that use the joints as support (e.g., backpacks) and being careful not to generate bruises (as the tissue recovery process takes longer). Furthermore, individuals affected by the Ehlers-Danlos Syndrome cannot do exercises that demand exaggerated strength because, as previously mentioned, it can cause displacement in the joint due to its hypermobility.

Because it is a syndrome that affects the formation of a basic component of the body, this condition affects its general integrity, thus having to be accompanied by a multidisciplinary team that includes a variety of professionals from physiotherapists to rheumatologists. Through this follow-up, the affected individual, in certain cases of hypermobile EDS, is instructed to use orthoses, to stabilize that joint and help with mobility, promoting an improvement in daily well-being.

4. Discussion

Collagen is present in connective tissues such as tendons, aponeuroses, cartilage, cornea of the eyes, skin and in the organic matrix of bones. Its structure is organized to provide resistance to the tissues it forms, with each type of collagen formed by a configuration corresponding to a specific level of rigidity and elasticity (Nelson et al., 2014) (Junqueira; Carneiro, 2017). In vertebrates, collagen composition is generally distributed as 35% Glycine (Gly), 21% Proline (Pro) and 4-Hydroxoproline (4-hyp) and 11% Alanine (Ala) (Nelson et al., 2014).

There are more than 40 types of collagens, the main ones being classified according to their function and organization. Fibrillar collagens come together to form collagen fibrils, which aggregate into bundles visible under an optical microscope as collagen fibers. Types I, II, III, V and XI collagens fall into this category, with I, III and V being important highlights in terms of understanding Ehlers-Danlos Syndrome (Junqueira; Carneiro, 2017) (Alberts et al., 2017). It is
important to highlight that the maintenance of mechanical resistance of fibril-forming collagen is related to covalent bonds that occur via lysyl oxidase.

Type I collagen is the most common type in connective tissue, constituting about 90% of the body’s total collagen, it is found in tendons, bones, skin, ligaments, internal organs and cornea, the same places where type I collagen is found. V. It is important to highlight the effects of the mutant phenotype on these types of collagens, essentially characterized by loose joints, fragile skin, and vessels susceptible to rupture (Alberts et al, 2017).

The individual affected by the pathology presents a mutation that affects the production of Type V, Type III, and Type I collagen, which affects the basic structure of the connective tissue of the human body, consequently causing weaknesses in the skin and in organs and other components of the body (Santos et al, 2021). The impairment caused by Ehlers-Danlos syndrome is mainly to the genes encoding protein chains, collagen-modifying proteins and the enzymes that process this chain (Espósito et al, 2016).

Firstly, it is worth highlighting that the collagens involved in Ehlers-Danlos Syndrome are fibrillar, that is, fibril-forming, structures formed by these proteins to present resistance to tension (Alberts et al, 2017). When leaving the cell environment, these fibrillar collagens form several polymers and organize themselves to provide the functionality established for this protein. Fibrillar collagen is composed of a triple helix and forms structures such as skin, bones, blood vessels, cartilage, etc. Fibril-forming collagens are types I, II, III, V (when with type I) and XI (when with type II), however the types most affected by EDS are types I, III and V, responsible, respectively, for bone synthesis, cartilage synthesis, and the formation of cartilage, vessels and skin (Alberts et al, 2017) (Kierszenbaum; Tres, 2016) (Malfait; Wenstrup; De Paepe, 2010).

In view of the above, the main damage caused at the molecular level by the dysfunction of collagen synthesis in patients affected by EDS is the formation of an incomplete structure of the collagen heterodimer, consequently affecting the formation of fibrils that, as already explained, make up the structures that resist tension and expansion in the human organism (Malfait; Wenstrup; De Paepe, 2010) (Ritelli; Colombi, 2020).
Of the 13 types of Ehlers-Danlos Syndrome, a subdivision is made into 6 main types and 7 rare types. In EDS Hypermobility, formerly type III, is the most common among the cases, there are signs that make it classified in the field of genetics as autosomal dominant, but its genetic basis is still unknown. Therefore, it does not require confirmation by genetic testing as it does not have a characteristic isolated gene (Ritelli; Colombi, 2020). In addition to hypermobility, patients with this type of EDS may suffer from postural orthostatic tachycardia and chronic joint pain (Santos et al, 2021).

Ehlers-Danlos syndrome is defined as genetic disorders that cause changes in collagen production and affect connective tissue, manifesting mainly through joint hypermobility, skin hyperextensibility and tissue laxity, such as joints, ligaments, skin, blood vessels, and internal organs (Lages; Lima; Ximenes, 2006).

When EDS is suspected, a complete physical examination is essential for identification, observing joint hypermobility and skin hyperextensibility. The diagnosis is made based on clinical and family history, physical examination, and genetic tests, among other tests, which vary depending on the type. Possible delays in diagnosis exacerbate symptoms and further harm the health of people with EDS, delaying treatment and causing a significant worsening of symptoms. To aid diagnosis, some tests are useful, such as clinical diagnosis, genetic test, complete blood count, coagulation tests, tilt table test, spinal x-ray (Espósito et al, 2016).

To improve their quality of life, many people affected by EDS use orthoses to stabilize hypermobile joints and mobility aids (canes, motorized wheelchairs, adapted vehicles, among others). As there is no definitive cure, treatment is based on preventive measures, established according to the patient’s needs. The rehabilitation and treatment process are extensive and requires multidisciplinary attention, with the help of various specialties, including a lot of physiotherapy, psychology, social assistance, among others (Miller, 2018).

In general, the problems caused in the routine of patients due to joint fragility due to the poor formation of the collagen fiber that make up the structures are in fact degrading, generating a unique need to modify the usual to avoid, for
example, dislocations shoulder or other areas occurs, limiting your freedom.

5. Conclusion

It can be inferred, then, regarding Ehlers-Danlos syndrome that it has its categories and divisions, which in total are thirteen classified types, with a substantial overlap of symptoms between the subtypes of EDS and other connective tissue disorders, including hypermobility spectrum disorders, as well as a lot of variability, therefore, an early and correct diagnosis, made with experts in the subject, is essential. This syndrome is a heterogeneous hereditary group of connective tissue diseases, exhibiting hyperextensibility of the skin, hypermobility of the joints, tissue fragility evident by easy bruising, and delayed healing with scars that do not atrophy.

This syndrome directly affects the fibrillar collagens, which are divided into 40 different types, but the most important in understanding this syndrome are I, III and VI. It is important to highlight that type I collagen covers 90% of the total collagen in the body, which largely encompasses this syndrome. The syndrome is a complex, multisystemic condition, where the great clinical challenge is the correct diagnosis. To achieve this, interdisciplinary cooperation must be encouraged and issues relating to clinical heterogeneity, disease classification, diagnosis and adequate treatment of pain must be addressed.

Despite its multisystem involvement, its main problems affect the joints in a way that makes them unstable and susceptible to dislocations or other more serious injuries. In this way, it limits the individual's life.

Treatment helps control symptoms and monitor the emergence of complications. Treatment options include medication, physiotherapy and, often, even surgery. Patients with EDS need monitoring by several professionals, such as a cardiologist, ophthalmologist, dermatologist, rheumatologist, and physiotherapist, given the multisystem impairment inflicted by the disease.

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