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A LITERATURE REVIEW ON PHYSICAL THERAPY MANAGEMENT OF A RARE CONDITION- EHLERS-DANLOS SYNDROME.

Physiotherapy & Rehabilitation

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ABSTRACT

Background: Ehlers Danlos syndrome is an autosomal dominant disorder characterized by hyper elasticity, fragility and hypermobility leading to pain and stiffness of the joints. EDS type iii exhibits a complex range of signs and symptoms of varying degree and combinations that make these conditions different to recognize. It is hypothesized that being hypermobile makes you more likely to develop chronic musculoskeletal pain due to an increased risk of re injury and experiencing more frequent pain**. Aim:** the aim of the present paper is to provide a state of understanding about the condition and a state of art od diagnosis and treatment of the present condition. **Methods:** PubMed, research gate, google scholar, science direct were the databases utilized to search for research papers. 67 articles of the past 22 years were collected and reviewed in accordance with the selection criteria. Selection criteria: individuals facing pain due to hypermobility were included as per the selection criteria. **Result:** from a total of 12 articles identified through the search, 42 articles were deemed eligible for the full text screening with 5 studies eligible to be included in this review. The result indicates management of hypermobility Ehlers Danlos syndrome poses challenges in definitively establishing the efficacy of physiotherapy as a reliable method for pain management in EDS patients. **Conclusion:** We draw inference from this literature study that findings underscore the need for comprehensive and multidimensional care strategies in addressing the complexity associated with EDS, especially in managing pain and enhancing patients wellbeing.

KEYWORDS

EDS, pain, hypermobility, hyper-elasticity.

INTRODUCTION:

Ehlers-Danlos Syndrome (EDS) an autosomal dominant disorder is a familial disorder of connective tissue characterized by hyper elasticity, fragility of skin, and hypermobility of the joints [1]. Symptoms can be highly debilitating in EDS [2]. The subjective interpretation of several semi quantitative clinical signs, such as joint hypermobility, skin hyper extensibility, tissue fragility, and bruising, however led to clinical uncertainty and diagnostic confusion regarding the type of EDS and the inclusion of the characteristically similar conditions under the broad diagnosis of EDS [3]. This study mainly considers the hypermobile type of EDS (hEDS). Hypermobile EDS was previously known as EDS type iii according to the berlin nosology [4] and EDS hypermobility type in Villefranche nosology [5]. EDS type iii exhibits a complex range of signs and symptoms of varying degree and combinations that make these conditions different to recognize [6]. Joint hypermobility is not a diagnosis but a description used to define a joint that exceeds its normal ROM taking into account age, sex and race [7,8]. The loss of hypermobility with age had been significantly demonstrated within the hypermobile population with the delineation of 3 distinct phases [9,10,11] hypermobility, pain stiffness characterized by a dramatic decrease in joint hypermobility with diminished quality of life [12].

In an study Sachet et al interviewed 51 patients with EDS of which 28(55%) were diagnosed with EDS hypermobile type they reported that the incidence of pain in hEDS WAS 28 out of 28 (100%) in this population the mean score on the numerical rating scale was 8 out of 10 for all types of EDS out of 28 patients 24 (85.7%) reported progressively worsening pain, the author concluded that moderate to severe pain is common in hEDS [13]. It is hypothesized that being hypermobile makes you more likely to develop chronic musculoskeletal pain due to an increased risk of re injury and experiencing more frequent pain [14]. Pain is the first symptom that occurs [15]. Musculoskeletal pain in EDS is influenced by external factors such as lifestyle, sports activities, trauma, surgery, and various comorbidities [15]. The most commonly reported pain areas are the neck, shoulder, knees and ankles [16,17]. The specific underling cause and mechanism of pain in EDS and particularly hEDS are not well understood but both acute and chronic pain are common manifestations and often contribute to disability [18].

However, there are many other signs and symptoms including neurophysiological involvement [19] muscle weakness [20] reduced proprioception [21,22] increased reflex latency [23] joint instability [24], and impaired balance [25]. Also, physical deconditioning and poor aerobic fitness are common findings in patients who are chronically unwell with hEDS proprioception [26,27] and balance [28] can be impaired which negatively influences body postures [14].

AIM:

the aim of the present paper is to provide a state of understanding about the condition and a state of art of diagnosis and treatment of the present condition.

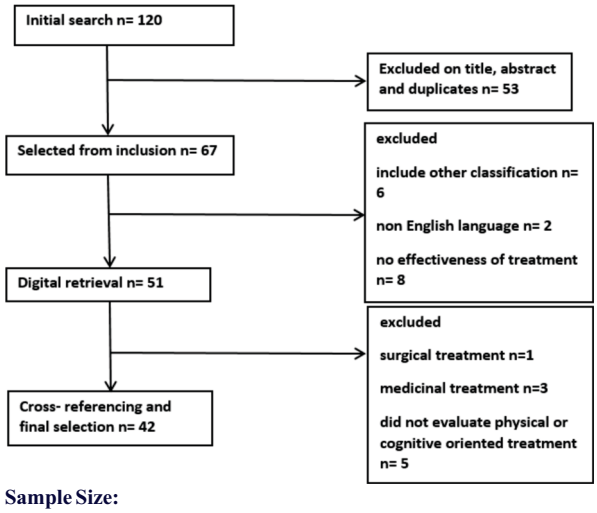
METHODOLOGY:

Study Design:

a comprehensive literature review was carried out on PubMed, Science direct to pinpoint studies related to chronic musculoskeletal pain, joint hypermobility, pain related fear, and disability. Cross- referencing of relevant articles was performed to ensure the inclusion of any potentially overlooked sources during the initial screening.

Search Strategy:

studies were initially identified through use of the search terms Ehlers-Danlos Syndrome, hypermobility, joint hypermobility, pain, beighton score, pain management, hypermobile EDS.



Sample Size:

Inclusion Criteria:

article that met the following criteria were included:

- Studies that were concentrated on joint hypermobility
- the studies that included pain that was caused by hypermobility in individuals
- the articles published between 1990-2022

- articles that concentrated more on adult population
- the published studies were in English language
- articles having full text

Exclusion Criteria:

- articles of past the year 1990
- articles including other types of Ehlers Danlos syndrome
- articles that included the surgical management
- articles that included children as their study criteria
- articles which did not contain data regarding musculoskeletal pain and its prevalence.

Selection Of Inclusion And Exclusion Criteria:

5 articles out of the 120 articles that met the inclusion and exclusion criteria were chosen for this analysis. For a comprehensive and accurate analysis only articles in English language articles were specifically selected. By focusing on English articles, the analysis potential deficiencies were reduced, as non- English articles have resulted in misunderstanding and collection of unrelated data. Articles published between 2000 and 2022 are included in this review. preference was given to full text articles to ensure extraction of information.

RESULT:

From a total of 120 articles identified through the search, 42 articles were deemed eligible for full text screening with 5 studies eligible to be included in this review. many international studies were identified, there were some RCTs studies all included studies were published during the last 23 years.

Reference	Population and setting	Intervention	N involved	Key outcomes
Zhou et al., 2018 [36]	hEDS	Goal- improve scapular motor control and decrease MDI, Months 1-3: isometric movements, shoulder abduction, internal and external rotations, extension and flexion Months 4-6 : the Watson programme for MDI	14 year female	Increase in active flexion, active abduction, stability after 6 months of interventions and positive sulcus sign at 6 – 12 months.
Palmer S et al (2021) [37]	Systemic review of RCTs	Exercises : RCTs measuring pain	283 participants (140 with intervention)	32/140 with significant reduction in pain relief in study subjects with intervention
Behnam Liaghat [38]	Long lasting shoulder symptoms	The exercise programme include five exercises targeting scapular and rotator cuff muscles, side lying external rotations, prone horizontal abductions, prone external rotation in 90^ of shoulder abduction, supine scapular protraction and shoulder elevation in scapular plane.	22 participants	Improvement in shoulder strength corresponded to 28-31% and clinical tests indicated shoulder laxity/instability
Pacey et al. (2013) [39]	Knee pain of no known aetiology	Physiotherapist supervised 8-week physical therapy program, including exercises to address muscle strength and motion control performed into the full range of knee hyperextension	29 participants (7-16 yrs.)	This study assesses various aspects related to knee pain in children, utilizing child-reported mean knee pain and parent-reported maximum knee pain over a week. Additionally, it examines the patients' global impression of change, functional ability measured by the Childhood Health Assessment Questionnaire (CHAQ), and quality of life using the Child Health Questionnaire. The study also delves into functional impairment through mean quadriceps and hamstring strength assessments.
Kemp et al. (2010) [40]	Arthralgia for at least 3 months preceding.	Physiotherapist supervised 6-week targeted physiotherapy programme, specifically addressing functional stability of symptomatic joints	57 participants (7 -16 yrs.)	This study gave us that there was a improvement in child's pain assessment score by the child as well as the parent , also there was an improvement in the functional ability of the child

Outcome Measures:

The five articles used a diverse outcome measures for their assessment. Pacey et al. (2013) employed the 100mm Visual Analogue Scale (VAS) for children pain intensity. Kemp et al. (2010) also used VAS, with children aged eleven and older self- reporting their pain, while those under eleven used the Wong-Baker Faces adaptation of VAS. Both studies utilized the Child Health Assessment Questionnaire (CHAQ) to assess physical functioning. BehnamLiaghat utilized the Western Ontario Stability Index (WOSI), Tampa Scale of Kinesiophobia-11 (TSK-11) to measure fear of movement, and the Global Perceived Effectiveness (GPE) scale to evaluate impression of recovery for shoulder exercises.

DISCUSSION:

The main subject of this study is to understand the significance of patients with hypermobile Ehlers- Danlos syndrome. the criteria for inclusion were the studies that were published between the year 1990 and 2020 that addressed the pain management strategies related with

hypermobility in individuals with EDS, considering bot pediatric and adult populations. for the final analysis, only articles that were in English and full texts were taken into account. given that pain is a prominent and frequent complaint among EDS patients, the purpose of this review is to ascertain the prevalence of pain in individuals with hEDS as well as a through description of sites and presentation of the condition. it was found that it is difficult to comprehend the unique makeup and distribution of pain in these individuals.

In the case of EDS pain can occur in a variety of forms, it can occur either in a general form or a musculoskeletal manifestation, and it can appear either as acute or chronic. the pain that is being experienced can be impacted by the external factors that includes the lifestyle choices, physical activity, trauma, operations, and other medical disorders. in a 2013 study by Castori et al. brought to light the first complaints of pain that patients had, which were generally related to joint injuries such as sprains and dislocations, as well the localized pain that was frequently attributed to the developing pain, which was mainly located in knees and thighs [14]. the knowledge of the cause and the underlying mechanism of pain in hEDS is insufficient. an important consideration in the diagnosis of this condition is clinical assessment, such as the Beighton assessment which is frequently used to assess joint hypermobility [34]. individuals with hEDS experience acute and chronic pain, which contributes to their impairment. Muscle spasm, involvement of tendon and connective tissue involvement, direct damage from the unstable joints, and nerve entrapment are all possible causes of pain. studies show that the patients localize their pain in areas such as the neck, shoulders, hip and lower extremities.

The limited evidence and dependence on expert opinions to guide the comprehensive management of hypermobile EDS are focused attention in this study. the key components of understanding and managing the condition is patient's education, physical and occupational therapy, psychological support along with the promotion of self-management. sue to the lack of approved treatment specifically for hypermobile EDS, a varied approach including physiotherapy, tailored exercises, lifestyle modifications, selected use of medications and surgical interventions may be effective in the treatment of the symptoms or the associated comorbidities. pain management strategies focus on addressing the underlying cause of pain and relieving its symptoms. in particular, empirical evidence shows that interventions to improve exercise over time have positive results in the context of treatment aimed at alleviating problems caused by joints immobility and instability. manual therapy to treat over active muscles, emphasis on core and trunk stability, posture correction, joint awareness through biofeedback for the enhancement of proprioception as well as correcting postural irregularities due to ligament laxity are part interventions in patients suffering from hEDS. aquatic therapy is quite beneficial in extreme situations. to lower the possibilities of subluxations or dislocations, gentle approach and strengthening exercises are recommended. systematically increasing the resistance, the exercise program concentrates on low resistance training with a progressive increase in repetition. addressing physical deconditioning and low aerobic fitness, which are frequently seen in individuals with joint hypermobility associated illnesses, is a crucial component of complete care given the intricate symptomatology associated with hypermobile EDS, the adoption of international classification of functioning, disability, and health (ICF) serves as an encompassing framework for understanding its complexity. there is a lack of convincing data to support specific exercise regimens, although there are some evidence suggesting that exercise may be beneficial for the treatment of hEDS symptoms. as of now, neither comparative studies nor randomized controlled studies have demonstrated the effectiveness of these routines for people with hEDS. toning exercises must be performed consistently and for an extended period of time in order to prevent progression pain deterioration while managing hEDS symptoms with exercise. it may take several years for significant pain reduction to manifest, highlight the gradual nature of improvement. when it comes to symptom management, people with hEDS tend to benefit from the concurrent and scheduled use of multiple medications.

CONCLUSION:

After reviewing various literature, it is found that Ehlers-Danlos syndrome is a very complex disorder that affects various organs, on a whole due to collagen abnormalities. Ehlers-Danlos syndrome has an impact on the tissues, skin and vasculature of the human body. There is a limited amount of literature focused on EDS, specifically hypermobile Ehlers-Danlos syndrome, which makes it difficult to determine physiotherapy as a beneficial method for pain management in the hypermobile patients.

The key literatures that were reviewed and analysed, suggested a lack of strong evidence supporting physiotherapy as an effective way to alleviate pain within this population. The existing evidence provides limited support for of exercise interventions in alleviating pain among the hypermobile patients. the Beighton score was the examination that was used for assessing and measuring hypermobility range in hypermobile patients. Alongside, pain was evaluated primarily using McGill pain questionnaire and the numerical rating scale across the selected articles.

Concluding, when treating the EDS patients multidimensional approach must be taken care of. This approach focuses on patients and caregiver's education, each patient's tolerance level and exercises tailored accordingly, strategies of pain management, addressing fatigue and stress, techniques of promoting self-management, utilizing splinting and bracing, and incorporating cognitive behavioural activities.

REFERENCES:

1. Ainsworth SR, Aulicino PL. A survey of patients with Ehlers-Danlos syndrome. Clin Orthop Relat Res. 1993 Jan;(286):250-6. PMID: 8425354.
2. Hakim A, O'Callaghan C, De Wandele I, Stiles L, Pocinki A, Rowe P. Cardiovascular autonomic dysfunction in Ehlers-Danlos Syndrome-Hypermobile type. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):168-174. doi: 10.1002/ajmg.c.31543. Epub 2017 Feb 4. PMID: 28160388.
3. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. 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.
4. Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, Hollister DW, Horton W, McKusick VA, et al. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. Am J Med Genet. 1988 Mar;29(3):581-94. doi: 10.1002/ajmg.1320290316. PMID: 3287925.
5. 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.
6. Yew KS, Kamps-Schmitt KA, Borge R. Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders. Am Fam Physician. 2021 Apr 15;103(8):481-492. PMID: 33856167.
7. Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):148-157. doi: 10.1002/ajmg.c.31539. Epub 2017 Feb 1. PMID: 28145606.
8. Grahame R. Joint hypermobility and genetic collagen disorders: are they related? Arch Dis Child. 1999 Feb;80(2):188-91. doi: 10.1136/adc.80.2.188. PMID: 10325741; PMCID: PMC1717821.
9. Castori M, Camerota F, Celletti C, Danese C, Santilli V, Saraceni VM, Grammatico P. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: a pilot study on 21 patients. Am J Med Genet A. 2010 Mar;152A(3):556-64. doi: 10.1002/ajmg.a.33231. PMID: 20140961.
10. Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type). Clin Exp Rheumatol. 2011 Nov-Dec;29(6):998-1005. PMID: 22208933.
11. Castori M, Dordoni C, Morlino S, Sperduti I, Ritelli M, Valiante M, Chiarelli N, Zanca A, Celletti C, Venturini M, Camerota F, Calzavara-Pinton P, Grammatico P, Colombi M. Spectrum of mucocutaneous manifestations in 277 patients with joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. Am J Med Genet C Semin Med Genet. 2015 Mar;169C(1):43-53. doi: 10.1002/ajmg.c.31425. Epub 2015 Feb 5. PMID: 25655071.
12. Malek, Sabeeha & Reinhold, Emma & Pearce, Gemma. (2021). The Beighton Score as a measure of generalised joint hypermobility. Rheumatology International. 41. 10.1007/s00296-021-04832-4.
13. Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manage. 1997 Aug;14(2):88-93. doi: 10.1016/s0885-3924(97)00007-9. PMID: 9262038.
14. van Meulenbroek T, Huijnen IPJ, Simons LE, Conijn AEA, Engelbert RHH, Verbunt JA. Exploring the underlying mechanism of pain-related disability in hypermobile adolescents with chronic musculoskeletal pain. Scand J Pain. 2020 Aug 31;21(1):22-31. doi: 10.1515/sjpain-2020-0023. PMID: 32862151.
15. Chopra P, Tinkle B, Hamonet C, Brock I, Gompel A, Bulbena A, Francomano C. Pain management in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):212-219. doi: 10.1002/ajmg.c.31554. Epub 2017 Feb 10. PMID: 28186390.
16. Adib N, Davies K, Grahame R, Woo P, Murray KJ. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology (Oxford). 2005 Jun;44(6):744-50. doi: 10.1093/rheumatology/keh557. Epub 2005 Feb 22. PMID: 15728418.
17. Johannessen EC, Reiten HS, Løvaas H, Maeland S, Juul-Kristensen B. Shoulder function, pain and health related quality of life in adults with joint hypermobility syndrome/Ehlers-Danlos syndrome-hypermobility type. Disability and Rehabilitation. 2016 Jul;38(14):1382-1390. DOI: 10.3109/09638288.2015.1102336. PMID: 26824670.
18. Tinkle B, Castori M, Berglund B, Cohen H, Grahame R, Kazkaz H, Levy H. Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-Danlos syndrome Type III and Ehlers-Danlos syndrome hypermobility type): Clinical description and natural history. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):48-69. doi: 10.1002/ajmg.c.31538. Epub 2017 Feb 1. PMID: 28145611.

19. Voermans NC, van Alfen N, Pillen S, Lammens M, Schalkwijk J, Zwarts MJ, van Rooij IA, Hamel BC, van Engelen BG. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Ann Neurol. 2009 Jun;65(6):687-97. doi: 10.1002/ana.21643. PMID: 19557868.
20. Rombaut L, Malfait F, De Wandele I, Mahieu N, Thijs Y, Segers P, De Paepe A, Calders P. Muscle-tendon tissue properties in the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken). 2012 May;64(5):766-72. doi: 10.1002/acr.21592. PMID: 22232076.
21. Smith TO, Jerman E, Easton V, Bacon H, Armon K, Poland F, Macgregor AJ. Do people with benign joint hypermobility syndrome (BJHS) have reduced joint proprioception? A systematic review and meta-analysis. Rheumatol Int. 2013 Nov;33(11):2709-16. doi: 10.1007/s00296-013-2790-4. Epub 2013 Jun 1. PMID: 23728275.
22. Hall MG, Ferrell WR, Sturrock RD, Hamblen DL, Baxendale RH. The effect of the hypermobility syndrome on knee joint proprioception. Br J Rheumatol. 1995 Feb;34(2):121-5. doi: 10.1093/rheumatology/34.2.121. PMID: 7704456.
23. Ferrell WR, Tennant N, Baxendale RH, Kusel M, Sturrock RD. Musculoskeletal reflex function in the joint hypermobility syndrome. Arthritis Rheum. 2007 Oct 15;57(7):1329-33. doi: 10.1002/art.22992. PMID: 17907144.
24. Rombaut L, Deane J, Simmonds J, De Wandele I, De Paepe A, Malfait F, Calders P. Knowledge, assessment, and management of adults with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type among Flemish physiotherapists. Am J Med Genet C Semin Med Genet. 2015 Mar;169C(1):76-83. doi: 10.1002/ajmg.c.31434. PMID: 25821093.
25. Rombaut L, Malfait F, De Wandele I, Thijs Y, Palmans T, De Paepe A, Calders P. Balance, gait, falls, and fear of falling in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken). 2011 Oct;63(10):1432-9. doi: 10.1002/acr.20557. PMID: 21793229.
26. Fatoye F, Palmer S, Macmillan F, Rowe P, van der Linden M. Proprioception and muscle torque deficits in children with hypermobility syndrome. Rheumatology (Oxford). 2009 Feb;48(2):152-7. doi: 10.1093/rheumatology/ken435. Epub 2008 Dec 16. PMID: 19088133.
27. Sahin N, Baskent A, Cakmak A, Salli A, Ugurlu H, Berker E. Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. Rheumatol Int. 2008 Aug;28(10):995-1000. doi: 10.1007/s00296-008-0566-z. Epub 2008 Mar 27. PMID: 18368409.
28. Schubert-Hjalmarsson E, Öhman A, Kyllerman M, Beckung E. Pain, balance, activity, and participation in children with hypermobility syndrome. Pediatr Phys Ther. 2012 Winter;24(4):339-44. doi: 10.1097/PEP.0b013e318268e0ef. PMID: 22965207.
29. Gensemer C, Burks R, Kautz S, Judge DP, Lavallee M, Norris RA. Hypermobile Ehlers-Danlos syndromes: Complex phenotypes, challenging diagnoses, and poorly understood causes. Dev Dyn. 2021 Mar;250(3):318-344. doi: 10.1002/dvdy.220. Epub 2020 Aug 17. PMID: 32629534; PMCID: PMC7785693.
30. Whalen KC, Crone W. Multidisciplinary Approach to Treating Chronic Pain in Patients with Ehlers-Danlos Syndrome: Critically Appraised Topic. J Pain Res. 2022 Sep 13;15:2893-2904. doi: 10.2147/JPR.S377790. PMID: 36124037; PMCID: PMC9482467.
31. Maarj M, Pacey V, Tofts L, Clapham M, Coda A. The Impact of Podiatric Intervention on the Quality of Life and Pain in Children and Adolescents with Hypermobility. Int J Environ Res Public Health. 2023 Aug 22;20(17):6623. doi: 10.3390/ijerph20176623. PMID: 37681763; PMCID: PMC10487040.
32. Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. Pain in ehlers-danlos syndrome is common, severe, and associated with functional impairment. J Pain Symptom Manage. 2010 Sep;40(3):370-8. doi: 10.1016/j.jpainsymman.2009.12.026. Epub 2010 Jun 25. PMID: 20579833.
33. Zabriskie HA. Rationale and Feasibility of Resistance Training in hEDS/HSD: A Narrative Review. J Funct Morphol Kinesiol. 2022 Aug 20;7(3):61. doi: 10.3390/jfmk7030061. PMID: 35997377; PMCID: PMC9397026.
34. Liaghat B, Skou ST, Jørgensen U, Sondergaard J, Søgaard K, Juul-Kristensen B. Heavy shoulder strengthening exercise in people with hypermobility spectrum disorder (HSD) and long-lasting shoulder symptoms: a feasibility study. Pilot Feasibility Stud. 2020 Jul 10;6:97. doi: 10.1186/s40814-020-00632-y. PMID: 32670599; PMCID: PMC7350677.
35. Mittal N, Sabo A, Deshpande A, Clarke H, Taati B. Feasibility of video-based joint hypermobility assessment in individuals with suspected Ehlers-Danlos syndromes/generalised hypermobility spectrum disorders: a single-site observational study protocol. BMJ Open. 2022 Dec 16;12(12):e068098. doi: 10.1136/bmjopen-2022-068098. PMID: 36526308; PMCID: PMC9764649.
36. Zhou Z, Rewari A, Shanthanna H. Management of chronic pain in Ehlers-Danlos syndrome: Two case reports and a review of literature. Medicine (Baltimore). 2018 Nov;97(45):e13115. doi: 10.1097/MD.0000000000013115. PMID: 30407326; PMCID: PMC6250522.
37. Micale L, Fusco C, Castori M. Ehlers-Danlos Syndromes, Joint Hypermobility and Hypermobility Spectrum Disorders. Adv Exp Med Biol. 2021;1348:207-233. doi: 10.1007/978-3-030-80614-9_9. PMID: 34807421.
38. Liaghat B, Skou ST, Jørgensen U, Sondergaard J, Søgaard K, Juul-Kristensen B. Heavy shoulder strengthening exercise in people with hypermobility spectrum disorder (HSD) and long-lasting shoulder symptoms: a feasibility study. Pilot Feasibility Stud. 2020 Jul 10;6:97. doi: 10.1186/s40814-020-00632-y. PMID: 32670599; PMCID: PMC7350677.
39. Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. Exercise in children with joint hypermobility syndrome and knee pain: a randomised controlled trial comparing exercise into hypermobile versus neutral knee extension. Pediatr Rheumatol Online J. 2013 Aug 14;11(1):30. doi: 10.1186/1546-0096-11-30. PMID: 23941143; PMCID: PMC3751568.
40. Peterson B, Coda A, Pacey V, Hawke F. Physical and mechanical therapies for lower limb symptoms in children with Hypermobility Spectrum Disorder and Hypermobile Ehlers-Danlos Syndrome: a systematic review. J Foot Ankle Res. 2018 Nov 7;11:59. doi: 10.1186/s13047-018-0302-1. PMID: 30455744; PMCID: PMC6222981.
41. Engelbert RH, Juul-Kristensen B, Pacey V, de Wandele I, Smeenk S, Woinarosky N, Sabo S, Scheper MC, Russek L, Simmonds JV. The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):158-167. doi: 10.1002/ajmg.c.31545. PMID: 28306230.
42. Ruiz Maya T, Fettig V, Mehta L, Gelb BD, Kontorovich AR. Dysautonomia in hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders is associated with exercise intolerance and cardiac atrophy. Am J Med Genet A. 2021 Dec;185(12):3754-3761. doi: 10.1002/ajmg.a.62446. Epub 2021 Jul 30. PMID: 34331416; PMCID: PMC8595563.
43. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. 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.