



Review Article

Hypermobile Ehlers-Danlos syndrome and rehabilitation: taking stock of evidence based medicine: a systematic review of the literature

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Abstract. [Purpose] The aim of the study was to conduct a systematic review about rehabilitation treatment of hypermobile Ehlers-Danlos syndrome, according to Evidence Based Medicine. [Methods] A systematic search has been conducted in following database: PubMed, PEDro, Cochrane, EDS Base Index, TRIP and CINHALL; no time restrictions were adopted. PICO method was employed to formulate the clinical query. Hypermobile Ehlers-Danlos syndrome and physiotherapy were the main keywords of the research. [Results] 1,869 articles emerged from the primary search. After duplicates removal, 1,709 papers have been screened by title and abstracts and then 1,698 were excluded following the inclusion criteria. 11 papers have been admitted to the last stage of the review and have been evaluated in their full-text version. Only one cohort study met the review's final step selection criteria. One cohort study on the efficacy of an integrated physiotherapeutic and cognitive behavioural treatment was evaluated by means of Newcastle-Ottawa Quality Assessment score and resulted of poor evidence. [Conclusion] At the present time, there is no Evidence Based Medicine literature on hypermobile Helers-Danlos syndrome rehabilitation. Clinical studies with high level of evidence are necessary in order to assess the efficacy of physiotherapeutic approaches. **Key words:** Ehlers-Danlos syndrome, Rehabilitation, Evidence-based medicine

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INTRODUCTION

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders (HCTDs). There are several types of EDS that may share some clinical symptoms as joint hypermobility, skin hyperextensibility and tissue fragility with high risk of internal organs' damage or prolapse¹⁾. The pathogenesis of the syndrome was studied by Mao et al.²⁾, who described three fundamental mechanisms: deficiency of collagen-processing enzymes, dominant-negative effects of mutant collagen α -chains, and haploinsufficiency. In the first two cases, the target organs of the pathology are skin, ligaments, tendons, oral structures, blood vessels and gastrointestinal system, while the reduced gene function in cases of haploinsufficiency brings about a general reduction in cell functions³⁾. At the present time 13 subtypes of EDS are known: classical, classical-like, cardiac-valvular, vascular, hypermobile, arthroclasia, dermatosparaxis⁴⁾, kyphoscoliotic, Brittle Cornea syndrome, spondylodysplastic, musculocontractural, myopathic and periodontal⁵⁾. The most widespread type of EDS is the hypermobile (hEDS), whose symptoms include joint hypermobility (affecting both large and small joints), soft and smooth skin that may be slightly elastic and bruises easily, and chronic musculoskeletal pain. Although hEDS shows a significant phenotypic overlap with the joint hypermobility syndrome (JHS), the two disorders should not be considered one and the same⁶⁾. The diagnosis of hEDS is clinical; the diagnostic criteria, as defined by Beighton et al.⁴⁾, are a general increase in joint range of motion (ROM) and an hyperextensible skin. This hyperextensibility may be verified by pulling the skin of the volar surface of the forearm until resistance is felt. Hypermobility of the joints is assessed on the Beighton score⁷⁾, which

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involves carrying out five tests:

1. Passive dorsiflexion of the fingers beyond 90°;
2. Passive retro-positioning of the thumbs until they make contact with the forearm;
3. Hyperextension of the elbow beyond 10°;
4. Hyperextension of the knee beyond 10°;
5. Forward flexion of the torso with the knees fully extended and the palms of the hands resting on the floor.

A point is allocated to each side in each of the tests, with the exception of the final one, with a maximum point score of 9. The diagnostic criteria have to be interpreted in line with the Brighton and Villefranche model⁸⁾ for hEDS (Table 1).

Rehabilitation and physical exercises are essential factors in the management of joint hypermobility, as various authors emphasise. In his descriptive text, Simmonds et al.⁹⁾ state that the therapeutic plan for hEDS can be divided into precocious and medium to long term stages. In the former, the work of the physiotherapist has to focus on awareness, proprioception and balance strategies, while in the more advanced treatment stage the emphasis has to be placed on eccentric and concentric muscle reinforcement. Alongside these general indications, the treatment plan also has to include sporting and water activities. In spite of the emphasis placed by various researchers on rehabilitative treatment of hEDS, no evidence based treatment protocols are currently available, as is pointed out by Russek¹⁰⁾.

The aim of this review is to assess the greater evidence currently available on the rehabilitative treatment of hEDS by carrying out a systematic review of the scientific literature.

METHODS

A systematic review of the literature was carried out in PubMed, PEDro, CINAHL, Cochrane, EDS Base Index and TRIP databases. No time restrictions were adopted. Access to the databases took place in July 2017. The PICO method was used to formulate the clinical query, on the basis of the following parameters:

- Population: patients with hypermobile Ehlers Danlos syndrome;
- Intervention: physiotherapy;
- Comparison: inactive control groups;
- Outcome: joint mobility and quality of life assessment scales.

The keywords used for the purpose of the primary search are summarised in Table 2.

The inclusion criteria for the second step of the review were as follow: studies on hEDS rehabilitation published in medical scientific journals. Papers on hypermobile syndromes of a different nature (e.g. Joint Hypermobility Syndromes–JHS) and those relating to publication types such as conference proceedings, extracts from textbooks and university essays were excluded. For the purpose of the review’s final step, only randomised controlled trials and cohort studies have been selected.

1,869 articles emerged from the primary search. First of all, all duplicates were removed and the remaining 1,709 papers

Table 1. Diagnostic criteria for EDS

Major criteria	Minor criteria
Beighton score $\geq 4/9$	Beighton score 1–3/9
Arthralgia for longer than >3 months in >4 joints	Arthralgia in 1–3 joints
	Hystory of joint dislocations
	>3 soft tissue lesions
	Marfanoid Habitus
	Skin striae, hyperextensibility, thin skin or abnormal scarring
	Ocular signs: drooping eyelids, myopia, antimongoloid slant
	History of varicose veins, pelvic prolapse or abdominal hernia

For the diagnosis both major criteria are needed, or a major and at least two minor ones, or four minor ones, or two minor criteria with a family history of hEDS.

Table 2. Keywords for the literary search

Keyword 1	Keyword 2	Boolean operator
Ehlers Danlos	Physiotherapy	And/Or
EDS-HT	Rehabilitation	
EDS	Physical exercise	
EDS hypermobility		
hEDS		

EDS: Ehlers Danlos Syndrome; HT: Hypermobile; h: hypermobyle.

have been screened by titles and abstracts. Then, 1,698 articles were excluded following the selection criteria and 11 have been admitted to the last stage of the review: 5 case reports, 1 cohort study and 5 investigative studies. Those 11 remaining papers have been read in full text version and evaluated by means of PEDro scale¹¹⁾ and/or Newcastle-Ottawa Quality Assessment score¹²⁾. Study selection was reported in Fig. 1.

RESULTS

The only study admissible to the final stage of the review was therefore the cohort study by Bathen et al.¹³⁾, which is also reported in Table 3. In this trial, the authors investigated the effects of a multidisciplinary rehabilitation program combining physical and cognitive-behavioural therapy in a cohort of 12 women with hEDS. The authors selected 12 patients for the trial with a Beighton score of $\geq 5/9$ or $\geq 4/9$ in association with joints' dislocations, chronic pain and skin extensibility of ≥ 2.5 cm. The treatment program consisted of two parts: (1) two and a half week in a rehabilitation unit with testing, physical training,

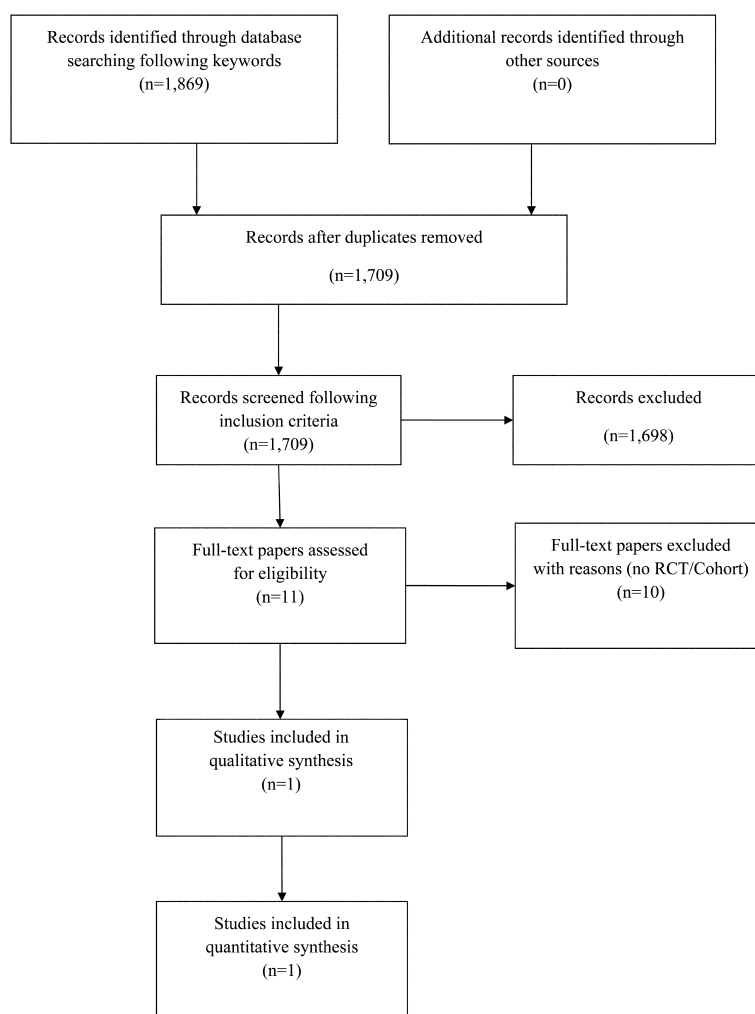


Fig. 1. Selection of articles for the review.

Table 3. Summary of included study

Study	Design	Participants	Intervention	Outcome measures
Bathen et al. (2013)	Cohort study	n=12	Strength training; body awareness exercises; core stability exercises; CBT therapy	<ul style="list-style-type: none"> • TSK scale for kinesiophobia • Stair walking up test • Stair walking down test • NRS

TSK: Tampa Scale of Kinesiophobia; CBT: Cognitive Behavioural Therapy; NRS: Numeric Rating Scale.

group discussions and lectures and (2) individual home exercises for three months with weekly guidance by local physiotherapist. The exercises, practiced three times a week, involved strength and resistance training for the limbs, acquisition of bodily awareness, and activation of core stability muscles. For the cognitive behavioural component, the various members of the multidisciplinary team alternated in information sessions in which they described the problem solving strategies to be implemented in everyday life (pain management, protection of the joints against excessive effort, movement optimisation). On completion of the hospital stay and home training period, the patients were reviewed by the team to assess the strategies learned by them. In the follow-up, the authors describe the improvement of patients in the activities of daily living (Canadian Occupational Performance Measure score), motor tests (upstairs and downstairs walking), pain (Numeric Pain Rating Scale), and kinesiophobia (Tampa Scale for Kinesiophobia-13). The authors therefore indicate a routine use of multidisciplinary physiotherapeutic and cognitive-behavioural treatment in hEDS. Newcastle-Ottawa Quality Assessment score for this paper was 2 points for selection items, 0 points for comparability ones, 2 for outcome. According to scoring system this was a poor quality study.

Five case reports investigated physiotherapeutic interventions in hEDS. Although these were not admitted to the final phase of the review, the protocols proposed within them have been analysed in brief below. In the double case report of La Tallec et al.¹⁴⁾, the effects of a rehabilitation training in two patients with hEDS were assessed. Although the authors did not specify the exercises and treatment intervals, they described an increase in the level of joint control and autonomy in the patients upon follow-up. They conclude by suggesting an hEDS treatment strategy combining physiotherapy, adoption of braces to prevent joint dislocation and correct patient education. Colloca et al.¹⁵⁾, on the other hand, proposed chiropractic treatment for two patients with hEDS. These patients, who suffered from pain in the extremities and biomechanical anomalies due to kyphoscoliosis, were assessed by means of the Oswestry Low Back Disability Index and Neck Disability Index, and were later treated by means of low energy spinal manipulation using the Chiropractic BioPhysics Technique protocols. The authors described an improvement in the points score in the two questionnaires used, and concluded by recommending the routine use of chiropractic manipulation in patients with hEDS. This indication was later taken up in the similar case report by Morley et al.³⁾. Camerota et al.¹⁶⁾ described neuromuscular taping applications in a patient with hEDS. Their paper reported a starting condition of severe pain during lumbar flexion and extension, accompanied by a structural weakness of the pelvic girdle. The patient was also subjected to gait analysis to assess the qualitative and quantitative characteristics of the gait cycle, which brought to light a short bilateral step and low cadence when walking. The intervention involved the application of neuromuscular taping at lumbar level and the knees for two weeks at three-weekly intervals. The final gait analysis showed an improvement in all the spatial and temporal parameters of the gait and a reduction in the pain experienced by the patient. Finally, in the case report by Bonandrini et al.¹⁷⁾, a patient with hEDS was studied following recurrent shoulder subluxation. The treatment involved multidisciplinary therapeutic (muscle pain techniques and neuromotor rehabilitation) and psychological interventions over a total period of 15 months. On completion of the treatment, the authors described an improvement on the scales of quality of life (Short Form-36), joint mobility (Disability of the Arm, Shoulder and Hand questionnaire) and kinesiophobia (Tampa Scale for Kinesiophobia), and went on to sustain a bio-psychosocial approach to hEDS.

DISCUSSION

This review is in line with the Prisma Statement¹⁸⁾ for systematic reviews. Given the shortage of studies, there are no sources of bias for discussion. It emerges from this review that there is no scientific evidence for hEDS rehabilitation. There are no RCT studies and the extremely rare testimonies in the literature nearly all relate to case reports¹⁴⁻¹⁷⁾. On the subject of physiotherapy for hypermobility, slight evidence was found for such pathologies as Joint Hypermobility Syndrome¹⁹⁾ (JHS, frequently found in differential diagnosis with hEDS). There are no randomised controlled trials which suggest and verify a specific rehabilitative setting for hEDS. In a scientific context of growing interest in rehabilitation of rare pathologies^{20, 21)}, the scientific community appears to be totally indifferent to physiotherapeutic approaches to hEDS. Although various authors emphasise the importance of rehabilitation for the prevention and management of the syndrome²²⁾, the literature is frequently limited to investigative studies. One example of this is the 2011 cross-sectional trial by Rombaut et al.²³⁾, which reports a retrospective investigation into the clinical and medical history of patients with hEDS. The author points out that in his case study 63.4% of patients treated with physiotherapy had a positive outcome in terms of pain (Visual Analogue Scale) and their general state of health (Sickness Impact Profile). In spite of this, no RCT has specifically investigated physiotherapeutic programmes, and the only work which emerged from the present survey¹³⁾ was a cohort study with no effective comparison which could confirm the authors' findings. It is therefore clear that randomised trials are absolutely essential if we are to verify the efficacy of conservative approaches.

At the present time, there is no scientific evidence for rehabilitation in hEDS. For this reason nowadays it's not possible to set up a general protocol for physiotherapeutic management of the syndrome. The authors trust that in the future this topic will be investigated and validated by an EBM literature based on RCT trials, in order to include physical therapy into the treatment guidelines of the hEDS with full rights.

Conflict of interest

None.

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