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Physical therapy treatment of hypermobile Ehlers–Danlos syndrome: A systematic review

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Abstract

Physiotherapy techniques are regularly prescribed in the hypermobile type Ehlers–Danlos syndrome (hEDS) and they are appreciated by the patients. The objective of this systematic review was to investigate the effect of the different physiotherapy techniques related to the children and adult patients with hEDS. PubMed, SPORTDiscus, Cochrane Library, PEDro, Scopus, and Embase databases were analyzed from inception to April 2020. Characteristics of the studies (authors), patients (sample size, sex, age, Beighton score), and nonpharmacological treatment (length of the program, number of session, duration of the session, and type of intervention), and the results with the dropout rate were extracted. From the 1045 retrieved references, 6 randomized controlled trial with a sample size ranging from 20 to 57 patients were included in the systematic review. There was a huge heterogeneity in the interventions. The durations of the program were from 4 to 8 weeks. Pain or proprioception demonstrated significant improvements in the intervention group regardless of the type of intervention. A benefit of the inspiratory muscle training was observed on functional exercise capacity. The quality of life was systematically improved. Physiotherapy benefits on proprioception and pain in patients with hEDS even if robust randomized control studies are missing.

KEYWORDS
Ehlers–Danlos, nonpharmacological, physiotherapy

1 | INTRODUCTION

Ehlers–Danlos syndrome (EDS) comprises a group of inherited connective tissue disorders that affect many body systems (gastrointestinal, cardiovascular, skeletal, and so on) (Byers & Murray, 2014). The 2017 international classification recognizes 13 clinical subtypes of EDS (Malfait et al., 2017). The hypermobile type Ehlers–Danlos syndrome (hEDS) is the most common subtype of the EDS (>80% of the case) and possibly the most common of all hereditary disorders of connective tissue. A distinction is now made between hEDS, isolated, nonsyndromic joint hypermobility and hypermobility spectrum disorders. The prevalence of hEDS is estimated to be over 2% in Caucasians (Fikree et al., 2013) and it affects more often women than men.

The patients with hEDS suffer from various musculoskeletal disorders such as tendinopathies, joint dislocation or subluxation, arthralgia, widespread pain, muscle weakness, gait abnormalities, or early onset osteoarthritis (Fikree et al., 2013; Rombaut et al., 2012; Scheper et al., 2017) but other clinical manifestations (digestive disorders, fatigue, etc.) can also be found (Bravo & Wolff, 2006; Voermans et al., 2011; Zeitoun et al., 2013). These patients are less active and present a reduced physical capacity with some functional limitations (Rombaut et al., 2010; Rombaut et al., 2012; Scheper et al., 2017). Even if many patients with hEDS have exertional dyspnea and

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breathing difficulties, the lung function cannot be considered as the cause (Reychler et al., 2019).

The approach in hEDS is holistic and the treatment focuses on the signs, symptoms, and complications of the patients. Despite the medications (>90% of the patients) and the surgery (>70% of the patients) are frequently prescribed, other nonpharmacological approaches are often proposed in hEDS (Rombaut et al., 2011). Indeed, apart from the psychological support, physiotherapy including physical exercise, neuromuscular electrical stimulation, hydrotherapy, massage, muscle and stability training, stretching, and manual therapy are regularly prescribed or used by the patients with hEDS to counteract the physical and functional impairments. Although the physiotherapy techniques are heterogeneous and the evidence for these treatments is mainly based on expert or expert committees' opinions, they are appreciated by the patients and showed a positive effect in 63.4% of cases (Rombaut et al., 2011).

The aim of this systematic review was to investigate the effect of the different physiotherapy techniques found in the literature and related to the children and adult patients with hEDS.

2 | METHODS

2.1 | Protocol

This systematic review was implemented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Based on this statement, the structured search, study selection, and risk-of-bias assessment of individual studies were included in this review.

2.2 | Search strategy

Two investigators (G. Reychler, M.-M. De Backer) performed the systematic search in PubMed, SPORTDiscus, Cochrane Library, PEDro, Scopus, and Embase databases from inception to end of April 2020. The search strategy used was defined with the PICOS criteria: Participants (Ehlers–Danlos, Joint hypermobility, Hypermobile syndrome) – interventions (physiotherapy techniques) – comparator (usual care or another exercises program) – Outcome (pain, proprioception, quality of life, functional capacity) – study design (randomized controlled trial). The search strategy was adapted to all databases. A secondary hand-searching from the reference lists of the retrieved articles as well as the use of the PubMed related articles option completed the database searches.

The terms related to the interventions (musculoskeletal manipulations, physiotherapy, physical therap*, rehabilitation, osteopathy, manual therap*, massage, exercis*, physical activit*, sport, physical training, strengthening, strength training, resistance training, stabilization, endurance, aerobic, balance, coordination, motor control, proprioception, hydrotherapy, treadmill, cycloergometer, walk*, swim*, relaxation, stretching, mind–body, tai chi, yoga, and qigong) were combined with them defining the disease (Ehlers–Danlos, joint hypermobility, hypermobil* syndrome).

2.3 | Inclusion and exclusion criteria

The randomized controlled trials evaluating the effects of nonpharmacological modalities in adult subjects diagnosed with hEDS were included.

The studies had to report at least one of the following parameters as outcome to be included: pain, proprioception, quality of life, impact on daily life, or functional or physical capacity. The articles published before the definition of the diagnostic criteria of hEDS (Beighton et al., 1998) and in other languages than English, Spanish, and French were excluded. Abstract-only papers were excluded. Studies reporting mixed data including patients with different diseases were also excluded.

2.4 | Study selection

Two independent reviewers (G. Reychler and M.-M. De Backer) identified the eligible studies and reviewed them against the selection criteria. Duplicates were removed before the screening. The retrieved studies were then screened based firstly on titles and abstracts and secondly on full-text articles. A third independent reviewer (G. Caty) resolved the disagreements in the selected studies.

2.5 | Data extraction and analysis

The extracted data were the characteristics of the studies (authors), patients (sample size, sex, age, and Beighton score), and nonpharmacological treatment (length of the program, number of sessions, duration of the session, and type of intervention) and the results with the dropout rate. Meta-analysis was not conducted due to the small number of studies retrieved and the heterogeneity in their respective interventions and outcomes. Therefore, this review focused only on description and qualitative synthesis of the identified studies.

2.6 | Risk of bias

The assessment of the methodological quality of the selected studies used the quality appraisal tool developed by Downs and Black. This tool comprises 27 questions (maximum total score of 28) and evaluates the quality of reporting (10 items), the external validity (3 items), the bias and confounding elements (13 items), and the statistical power (1 item) of all the studies (O'Connor et al., 2015). A grade ranging from "poor" (<14 points) to "excellent" (24–28 points) was assigned to each study evaluated by this quality appraisal tool (O'Connor et al., 2015).

3 | RESULTS

3.1 | Studies selection

The process of studies selection is highlighted in the PRISMA flowchart (Figure 1). One thousand and forty-five references were retrieved from the different databases and other sources. After duplicates removal, 525 items were screened with titles and abstracts, from which 12 were read in with full-text. From this analysis, six randomized controlled trial were included in the systematic review to the qualitative analysis (Daman et al., 2019; Kemp et al., 2010; Pacey et al., 2013; Reychler et al., 2019; Sahin et al., 2008; Toprak Celenay & Ozer Kaya, 2017). The reasons for exclusion are highlighted in Figure 1.

3.2 | Characteristics of the studies and patients

The characteristics of the studies are presented in Table 1. All the retrieved studies comprised a sample size ranging from 20 to 57 patients, with a total of 212 patients recruited. Among the patients included, there were mainly women (from 65% to 100%) in the studies. The mean age of the patients ranged from 10.9 to 49.5 years and two studies were performed in children. The mean Beighton score was 6.4 and ranged from 5.7 to 7.6 but two studies did not mention this score (Daman et al., 2019; Sahin et al., 2008).

3.3 | Intervention

There was a huge heterogeneity in the interventions evaluated. The muscle training was the most frequent intervention with exercise to improve the proprioception. The interventions mainly focused on the lower limbs even if one of them targeted the inspiratory muscles. Two out of the studies proposed interdisciplinary programs with therapeutic education sessions. Only one study compared two different modalities. All physiotherapy programs but one were supervised.

The durations of the program were from 4 to 8 weeks. The number of sessions by week were highly variable and varied from 1 to 5 sessions. The duration of the sessions was between 30′ and 60′. The dropout rate was relatively important in two studies along one with showing a dropout rate higher than 25% (Kemp et al., 2010). The dropout rate was low or unreported in the other studies.

3.4 | Results

All the results are summarized in Table 2. All the studies evaluating pain (Daman et al., 2019; Kemp et al., 2010; Pacey et al., 2013; Sahin et al., 2008; Toprak Celenay & Ozer Kaya, 2017) or proprioception (Daman et al., 2019; Sahin et al., 2008) demonstrated significant difference between intervention and control groups and improvements were only observed in the intervention group. Moreover, the

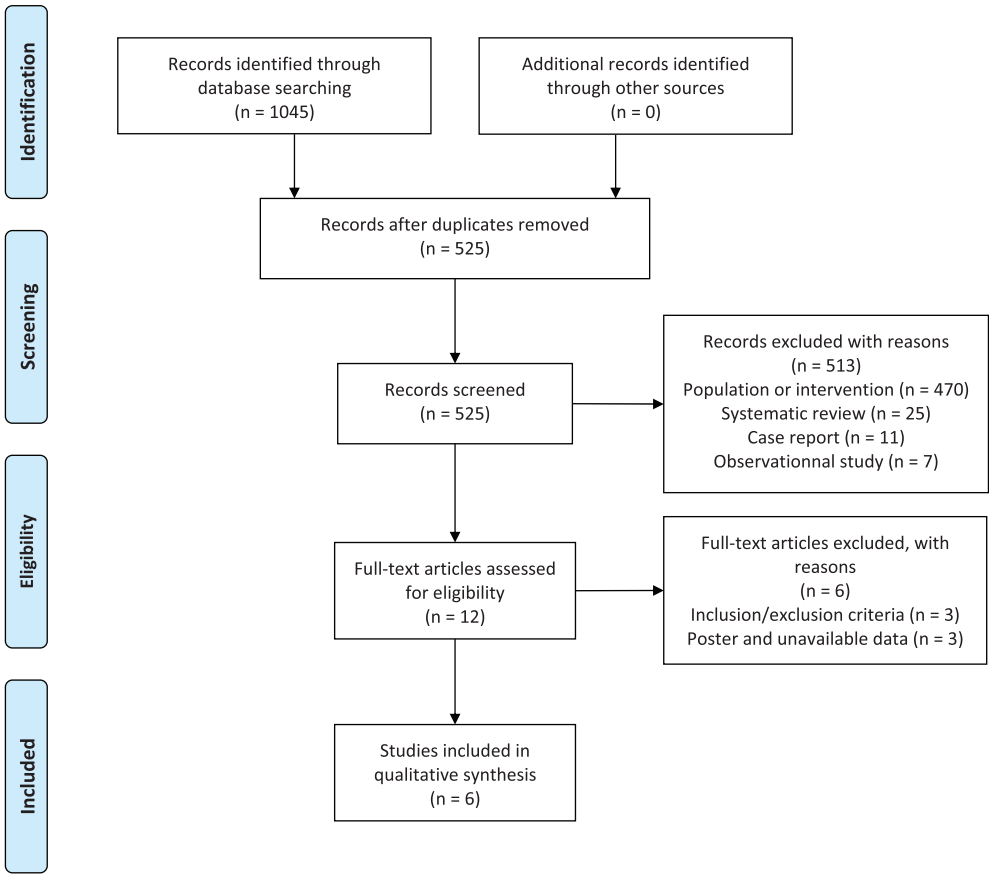

FIGURE 1 PRISMA flowchart

TABLE 1 Characteristics of the selected studies

Author	Population	Intervention and comparator		Outcomes	Dropout (%)
Sahin (18)	*N* (%F) = 40 (85) 26.9 ± 7.1y BS: NA	8 weeks 24 sessions ≈30′/session Supervised	IG (*n* = 15): kinesthesia and exercises of balance CG (*n* = 25): usual care	Pain (VAS) Proprioception (Isokinetic Dynamometer) Impact (AIMS-2)	0
Kemp (16)	*N* (%F) = 57 (66) 10.9 ± 2.5y BS: 5.8 ± 1.6	6 weeks 6 sessions ≈30′/session Partly supervised	IG (*N* = 30): targeted program correcting motion control of symptomatic joints CG (*N* = 27): generalized physical activity program of graded exercises	Pain (VAS + Wong Baker scale) Functional exercise capacity (6MWT) Pain (VAS parents) Impact (VAS parents) Functional abilities in daily living activities (CHAQ parents)	28
Pacey (17)	*N* (%F) = 25 (65) 12 ± 2.9y BS: 7.4 ± 1.2	8 weeks 6 sessions 30–60′/session Supervised	IG (*N* = 11): competency-based progressive physiotherapy program focused on improving strength and control around the knee joint into knee hyperextension range CG (*N* = 14): competency-based progressive physiotherapy program focused on improving strength and control around the knee joint into neutral knee extension	Pain (VAS) Impact of the intervention (PGIC) Strength (LL) (hand-held dynamometer) Functional abilities in daily living activities (CHAQ) 2′ step test Parents reported HRQoL (CHQ)	4
Daman (15)	*N* (%F) = 24 (100) 22.2 ± 1.3y BS: NA	4 weeks 12 sessions ≈30′/session Supervised	IG (*N* = 12): combined therapy with closed kinetic chain exercises and proprioception exercises CG (*N* = 12): usual care	Pain (VAS) Proprioception (Isokinetic Dynamometer) QoL (SF36)	NR
Toprak (19)	*N* (%F) = 46 (100) 20.6 ± 2.2y BS = 7.6 ± 1.0	8 weeks 24 sessions 40–45′/session Supervised	IG (*N* = 18): spinal stabilization exercise CG (*N* = 20): usual care	Pain (VAS) Endurance (muscle) (McGill test) Postural stability (Biodex Balance System)	21
Reychler (11)	*N* (%F) = 20 (100) 49.45 ± 4.45y BS: IG 5.9 ± 0.7 CG: 5.7 ± 0.5	6 weeks 30 sessions 6 × 10 repetitions/session Nonsupervised	IG (*N* = 9): inspiratory muscle training (threshold) CG (*N* = 10): usual care	Inspiratory muscle strength (SNIP) Lung function Functional exercise capacity (6MWT) Anxiety and depression (HADS)	5

Note: Mean ± *SD*.

Abbreviations: %F, percentage of women; 6MWT, 6 minute walking test; AIMS-2, Arthritis Impact Measurement Scales-2; BS, Beighton score; CG, control group; CHAQ, Childhood Health Assessment Questionnaire; CHQ, Childhood Health Questionnaire; HADS, Hospital Anxiety Depression Scale; IG, intervention group; *N*, sample size; NR, nonreported; PGIC, Patient's Global Impression of Change; SF36, 36-item Short Form Health Survey; SNIP, sniff nasal inspiratory pressure; VAS, visual analog scale.

improvements in the intervention group were observed regardless of the type of intervention.

In the studies comparing two exercises program, the investigated treatment demonstrated better result than the comparative group (Kemp et al., 2010; Pacey et al., 2013). The benefits were maintained after 3 months postintervention in one study (Kemp et al., 2010).

The changes in functional aspects varied according to the evaluation tools and the intervention program investigated in the studies. A benefit of the inspiratory muscle training was observed on functional exercise capacity measured using the 6 minute walking test (6MWT) compared to a control group (Reychler et al., 2019). Conversely, two other studies failed to show a benefit on functional exercise capacity (quantified by maximal field test) after different programs of exercises (Kemp et al., 2010; Pacey et al., 2013). In these studies, the effect was quantified by field test that can be considered as maximal test. Some domains from global questionnaires (Arthritis Impact Measurement Scales-2 [AIMS-2; Sahin et al., 2008], Childhood Health Questionnaire [CHQ; Pacey et al., 2013], SF-36 [Daman et al., 2019]) focused on functional or physical status of the patients.

TABLE 2 Results of the selected studies

		IG			CG			Intergroup difference
Author	**Outcomes (unit)**	**Pre**	**Post**	***p*-value**	**Pre**	**Post**	***p*-value**	***p*-value**
Sahin (18)	VAS at rest (cm)	3.27 ± 2.49	1.83 ± 0.72	0.027	3.48 ± 2.06	3.44 ± 2.04	0.317	/
	VAS during exercise (cm)	5.87 ± 2.35	3.27 ± 2.49	0.010	5.96 ± 1.83	5.88 ± 1.90	0.157	/
	Isokinetic dynamometer (left) (angle error)	2.42 ± 0.68	1.12 ± 1.70	0.001	2.40 ± 0.69	2.40 ± 0.69	0.743	/
	Isokinetic dynamometer (right) (angle error)	2.73 ± 0.80	1.83 ± 0.72	0.001	2.38 ± 0.59	2.41 ± 0.59	0.586	/
	AIMS-2 (physical)	1.58 ± 1.31	1.21 ± 1.35	0.358	1.31 ± 1.14	1.27 ± 1.24	0.891	/
	AIMS-2 (emotional)	4.15 ± 2.18	3.85 ± 1.62	0.596	4.31 ± 1.68	4.64 ± 2.24	0.589	/
	AIMS-2 (symptoms)	3.70 ± 2.69	2.53 ± 2.44	0.206	4.66 ± 2.91	3.76 ± 2.51	0.185	/
	AIMS-2 (social)	3.11 ± 1.53	3.05 ± 1.64	0.917	3.04 ± 1.71	2.96 ± 1.88	0.867	/
	AIMS-2 (functional)	2.96 ± 2.99	1.12 ± 1.70	0.006	3.06 ± 1.86	2.14 ± 2.46	0 0.117	/
Kemp (16)	VAS + Wong Baker scale (mm)	55.53 ± 21.32	31.77 ± 23.37	0.026	62.09 ± 24.14	39.82 ± 26.01	0.009	0.48
	Modified 6MWT (×9 m)	94.90 ± 22.18	92.48 ± 26.81	0.33	79.41 ± 23.14	77.88 ± 21.73	0.84	0.72
	VAS parents (pain) (mm)	45.12 ± 22.97	19.44 ± 20.59	0.002	48.44 ± 22.88	36.00 ± 24.77	0.052	0.97
	VAS parents (impact) (mm)	36.05 ± 26.44	17.74 ± 22.18	0.021	37.24 ± 25.27	33.60 ± 26.02	0.54	0.667
	CHAQ	0.62 ± 0.65	0.46 ± 0.56	0.037	0.76 ± 0.68	0.83 ± 0.68	0.25	0.577
Pacey (17)	VAS (mm)	38.55 ± 16.89	29.36 ± 17.99	0.004*	40.04 ± 16.59	20.14 ± 18.37		0.246
	PGIC	0.18 ± 0.87	1.82 ± 0.75	<0.001*	0.29 ± 1.14	1.71 ± 0.99		0.675
	Hand-held dynamometer (N)	4.38 ± 2.37	5.59 ± 1.45	0.004*	4.02 ± 1.72	4.90 ± 2.17		0.608
	2′ step test (*n*)	20.88 ± 6.69	20.55 ± 5.44	0.11*	16.32 ± 5.00	20.11 ± 5.52		0.118
	CHAQ	0.04 ± 0.71	0.05 ± 0.72	0.433*	−0.13 ± 0.44	−0.01 ± 0.60		0.552
	CHQ (physical)	41.61 ± 14.96	43.91 ± 15.05	0.002*	32.01 ± 11.86	42.08 ± 10.81		0.037
	CHQ (psychosocial)	46.29 ± 8.95	54.41 ± 4.42	0.03*	46.35 ± 12.26	45.41 ± 133.49		0.09
Daman (15)	VAS (cm)	4.98 ± 1.32	2.25 ± 1.48	0.001	4.87 ± 1.86	5.37 ± 2.07	0.2	<0.001
	Isokinetic dynamometer (without load) (angle error)	3.84 ± 3.68	2.07 ± 1.81	0.01	4.90 ± 3.41	5.02 ± 3.05	0.7	0.009
	Isokinetic dynamometer (with load) (angle error)	6.24 ± 5.39	2.53 ± 2.71	0.005	5.62 ± 4.43	5.69 ± 4.69	0.92	0.03
	SF-36 (physical)	59.90 ± 6.28	71.89 ± 9.39	0.001	60.50 ± 9.70	60.55 ± 9.55	0.94	0.01
	SF-36 (mental)	57.39 ± 16.75	58.05 ± 17.06	0.31	51.80 ± 17.49	52.56 ± 13.63	0.69	0.42
Toprak (19)	VAS (cm)	1.6 [0.0–10.0]	0.0 [0.0–0.0]	0.001	0 [0–6]	0 [0–6]	0.208	0.022
	Flexion (s)	22 [10–77]	53 [20–118]	0.003	38 [16–58]	39 [12–60]	0.255	<0.001
	Extension (s)	27 [8–100]	59 [15–140]	<0.001	40 [6–77]	45 [8–120]	0.379	0.003
	Right lateral flexion (s)	30.5 [12–70]	58.5 [30.0–50.0]	0.001	40 [12–103]	40 [17–104]	0.589	0.001
	Left lateral flexion (s)	30.0 [11–82]	56.5 [34–125]	<0.001	42 [13–90]	42.5 [1–106]	0.705	<0.001
	Static mode eyes open	0.9 [0.4–4.7]	1.0 [0.2–2.0]	0.076	1.0 [0.1–3.4]	0.6 [0.1–1.2]	0.061	0.884

TABLE 2 (Continued)

Author	Outcomes (unit)	IG			CG			Intergroup difference
		Pre	Post	*p*-value	Pre	Post	*p*-value	*p*-value
	Static mode eyes closed	1.5 [0.3–4.7]	1.2 [0.3–2.7]	0.028	1.4 [0.4–4.7]	1.1 [0.3–5.7]	0.379	0.447
	Dynamic mode eyes open	0.9 [0.5–2.1]	0.6 [0.3–3.9]	0.075	0.7 [0.4–2.7]	0.8 [0.7–2.7]	0.306	0.036
	Dynamic mode eyes closed	4.3 [1.2–8.1]	2.8 [1.3–5.4]	0.008	3.4 [0.4–6.0]	2.7 [1.2–6.5]	0.653	0.070
Reychler (11)	SNIP (cm H_2O)	41 ± 17	49 ± 18	0.03	41 ± 19	38 ± 20	0.088	<0.001
	FVC (%)	115 ± 20	116 ± 17	0.716	110 ± 13	103 ± 18	0.047	0.237
	FEV1 (%)	94 ± 14	103 ± 11	0.010	92 ± 21	89 ± 23	0.241	0.009
	6MWT (m)	455 ± 107	515 ± 127	0.036	444 ± 128	465 ± 131	0.195	0.003
	HADS-A	11 ± 3	7 ± 4	0.115	10 ± 5	10 ± 4	0.583	0.83
	HADS-D	7 ± 3	6 ± 4	0.951	7 ± 4	7 ± 5	0.116	0.408

Note: Mean ± *SD* or median [min–max].

Abbreviations: 6MWT, 6 minute walking test; AIMS-2, Arthritis Impact Measurement Scales-2; CG, control group; CHAQ, Childhood Health Assessment Questionnaire; CHQ, Childhood Health Questionnaire; HADS, Hospital Anxiety Depression Scale; IG, intervention group; P, parents; PGIC, Patient's Global Impression of Change; SF36, 36-item Short Form Health Survey; SNIP, sniff nasal inspiratory pressure; VAS, visual analog scale.

*p-Values correspond to the effect of the two mixed intervention groups.

The quality of life was better in the intervention group compared to the control group after the sessions but only the physical domain (Daman et al., 2019) and it improved with the interventions when it was included in the outcomes (Daman et al., 2019; Pacey et al., 2013). In the study comparing two exercises program into different range of motion, patients exercising into the hypermobile range showed a greater benefit in the psychosocial summary score of the CHQ and in self-esteem, behavior, and mental health domains, and a lower improvement in the physical summary score than the subjects exercising into their neutral range (Pacey et al., 2013).

The muscular endurance was improved by static exercises compared to the control group whatever the muscular group evaluated (Toprak Celenay & Ozer Kaya, 2017). An improvement was only observed in the intervention group. Only one study assessing the effect of inspiratory muscle training focused on the lung function and inspiratory muscle strength and showed an improvement in these outcomes (Reychler et al., 2019).

3.5 | Quality assessment of the studies

The Downs and Black scores are shown in Table 3. The median score of the studies was 21.5/28 and it ranged from 18 to 23/28. One study was classified as "Fair" and the others were considered as "Good."

4 | DISCUSSION

This is the first systematic review on the physical treatments of patients with hEDS even if there was one focusing on children and including the two of our retrieved studies (Peterson et al., 2018). Our results highlight the paucity of randomized clinical trials on the physical treatment in hEDS although the retrieved studies were methodologically well-designed. Pain and proprioception were the most consistently reported outcomes and the results of these studies are univokely positive in comparison of usual care. They showed that these two outcomes improved whatever the physical treatment proposed both in children and adult patient with hEDS.

Due to the lack of proprioception observed in these patients (Robbins et al., 2020), specific exercises should be included in the treatment since an improvement was systematically observed in the three studies reporting this important outcome (Daman et al., 2019; Sahin et al., 2008; Toprak Celenay & Ozer Kaya, 2017). Although, the improvement was statistically significant in comparison with control group in two studies, one study did not report the intergroup comparison. These exercises are design to restore the motor control of lower limbs and to maintain a good balance. Pain is also an important symptom in this disease since 90% of patients with hEDS are concerned (Voermans et al., 2010). Then, it is not surprising to find it as outcome in many studies. However, it is worth to be note that only the sensory domain of pain was assessed in different studies. An intergroup difference on pain was observed in all the studies performing such a comparison (Daman et al., 2019; Toprak Celenay & Ozer Kaya, 2017). Until now, the underlying mechanisms of pain in hEDS are poorly understood even if nociceptive and neuropathic pain, impaired proprioception, muscle weakness, and central sensitization are likely contributing factors. Then, the pain improvement could be related to the benefit observed in proprioception. Moreover, a relationship between pain and proprioception improvements was demonstrated (Ferrell et al., 2004; Revivo et al., 2019). Indeed, the proprioception helps to protect against the damage related to hyperextension. Different physiotherapy modalities were demonstrated to be beneficial on the mechanisms of pain.

As expected, due to the well-known consequences of this disease on the cardiorespiratory system, three studies focused on cardiorespiratory consequences of the disease by assessing the functional exercise capacity (Kemp et al., 2010; Pacey et al., 2013; Reychler et al., 2019). Only one study compared intervention and a control group and showed an intergroup difference on this outcome (Reychler et al., 2019). The walked distance improved only after 6 weeks in the inspiratory muscle training group compared to the control group and the gain suggests a clinically effect even if no minimal clinically important difference was determined in this population for 6MWT. Cardiovascular-related autonomic dysfunctions have been observed in more than 20% of these patients (Krahe et al., 2018). In addition, the sedentary lifestyle of these patients related to pain, fatigue, and hypermobility and instability of joints may cause muscle weakness (Reychler et al., 2019), thereby justifying more robust evaluation of the effect of physical exercise following the model of pulmonary rehabilitation. The poor respiratory muscle function observed in these patients reinforces this opinion. Postural orthostatic tachycardia syndromes that are characterized by an excessive heart rate increase were associated to EDS (Wallman et al., 2014). Moreover, the postural orthostatic tachycardia syndrome improved after exercises program

TABLE 3 Quality results of the selected studies evaluated by the downs and Black quality tool

	Study quality (10)	External validity (3)	Study bias (7)	Confounding and selection bias (6)	Power (1)	Total/ 28
Sahin (18)	7	2	6	5	1	21
Kemp (16)	8	2	5	5	1	20
Daman (15)	7	1	6	3	1	18
Pacey (17)	9	3	5	5	1	23
Toprak (19)	8	1	6	5	1	21
Reychler (11)	8	1	7	5	1	22

(Fu et al., 2011; Shibata et al., 2012). Altogether, these elements could explain the notable benefit of a specific cardiorespiratory exercise program in patients with hEDS.

The quality of life is an important outcome in patients with hEDS. Surprisingly, it was not frequently included in the outcomes of the retrieved studies. It is then difficult to state on this outcome due to the lack of data even if the only study focusing on an intergroup comparison demonstrated a benefit (Daman et al., 2019).

Only six randomized clinical trials about the non-pharmacological treatment in hEDS were retrieved in the different database. Similar results to these studies were found in observational studies that also showed benefits (Ferrell et al., 2004; Revivo et al., 2019). However, such observational studies cannot avoid the Hawthorne effect implying that individuals modify an aspect of their behavior in response to their awareness of being observed. This effect could influence the results of observational studies or control groups in this disease because the expectations of the patients are high due to the lack of awareness, heterogeneity of clinical presentation, and reliance on physical examination for diagnosis which generate misunderstandings (Grahame, 2013; Kumar & Lenert, 2017). However, Ferrell et al. assessed the patients at three moments (at inclusion, after a "no intervention" period, and after the intervention) and a benefit was observed for strength, proprioception, balance, and quality of life only after the intervention but not after the period free of treatment (Ferrell et al., 2004). These results reinforce the idea that neither Hawthorne effect nor training effect can explain the benefits observed in the studies.

Two studies compared the effect of two different modalities of treatment and found no difference between them (Kemp et al., 2010; Pacey et al., 2013). If we consider that the benefit of physiotherapy techniques is evident based on the results of the other included studies, thus the optimal settings remain to be determined. Further studies should focus on this element.

Despite the supervision found in a lot of studies, the rate of dropout was dramatically high even if it was discordant between studies. This high dropout rate was mainly due to the nonattendance of the patients to the sessions. Such dropout rate was already observed in this population of patients (To & Alexander, 2019). Different hypothesis can explain this rate such as unfulfilled needs of the patients, great number of medical visits, and distance from home to the center. This element has to be taken into account in further studies and barriers generating this high rate should be understood to improve the adherence.

Some limitations must be addressed in relation to this systematic review. The main limitation is the influence of the diagnosis. Indeed, new criteria to make a distinction made between hEDS, isolated, non-syndromic joint hypermobility, and hypermobility spectrum disorders were established only recently (Malfait et al., 2017). Before this date, some patients could have been included based on other criteria. Another limitation is the small number of studies and the heterogeneity of their interventions and outcomes which precluded any meta-analysis. The high rate of dropout is also a potential limiting factor.

In conclusion, even if this systematic review suggests a benefit of physiotherapy on proprioception and pain in patients with hEDS, it highlights the lack of robust randomized control studies.

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CONFLICT OF INTEREST

All authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Beighton, P., De Paepe, A., Steinmann, B., Tsipouras, P., & Wenstrup, R. J. (1998). Ehlers-Danlos syndromes: Revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *American Journal of Medical Genetics*, *77*(1), 31–37. https://doi.org/10.1002/(sici)1096-8628(19980428)77:1<31::aid-ajmg8>3.0.co;2-o

Bravo, J. F., & Wolff, C. (2006). Clinical study of hereditary disorders of connective tissues in a Chilean population: Joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. *Arthritis and Rheumatism*, *54*(2), 515–523. https://doi.org/10.1002/art.21557

Byers, P. H., & Murray, M. L. (2014). Ehlers-Danlos syndrome: A showcase of conditions that lead to understanding matrix biology. *Matrix Biology*, *33*, 10–15. https://doi.org/10.1016/j.matbio.2013.07.005

Daman, M., Shiravani, F., Hemmati, L., & Taghizadeh, S. (2019). The effect of combined exercise therapy on knee proprioception, pain intensity and quality of life in patients with hypermobility syndrome: A randomized clinical trial. *Journal of Bodywork and Movement Therapies*, *23*(1), 202–205. https://doi.org/10.1016/j.jbmt.2017.12.012

Ferrell, W. R., Tennant, N., Sturrock, R. D., Ashton, L., Creed, G., Brydson, G., & Rafferty, D. (2004). Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. *Arthritis and Rheumatism*, *50*(10), 3323–3328. https://doi.org/10.1002/art.20582

Fikree, A., Aziz, Q., & Grahame, R. (2013). Joint hypermobility syndrome. *Rheumatic Diseases Clinics of North America*, *39*(2), 419–430. https://doi.org/10.1016/j.rdc.2013.03.003

Fu, Q., Vangundy, T. B., Shibata, S., Auchus, R. J., Williams, G. H., & Levine, B. D. (2011). Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome. *Hypertension*, *58*(2), 167–175. https://doi.org/10.1161/HYPERTENSIONAHA.111.172262

Grahame, R. (2013). Joint hypermobility: Emerging disease or illness behaviour? *Clinical Medicine (London)*, *13*(Suppl 6), s50–s52. https://doi.org/10.7861/clinmedicine.13-6-s50

Kemp, S., Roberts, I., Gamble, C., Wilkinson, S., Davidson, J. E., Baildam, E. M., Cleary, A. G., McCann, L. J., & Beresford, M. W. (2010). A randomized comparative trial of generalized vs targeted physiotherapy in the management of childhood hypermobility. *Rheumatology*

(*Oxford*), *49*(2), 315–325. https://doi.org/10.1093/rheumatology/kep362

Krahe, A. M., Adams, R. D., & Nicholson, L. L. (2018). Features that exacerbate fatigue severity in joint hypermobility syndrome/Ehlers-Danlos syndrome - hypermobility type. *Disability and Rehabilitation*, *40*(17), 1989–1996. https://doi.org/10.1080/09638288.2017.1323022

Kumar, B., & Lenert, P. (2017). Joint hypermobility syndrome: Recognizing a commonly overlooked cause of chronic pain. *The American Journal of Medicine*, *130*(6), 640–647. https://doi.org/10.1016/j.amjmed.2017.02.013

Malfait, F., Francomano, C., Byers, P., Belmont, J., Berglund, B., Black, J., Bloom, L., Bowen, J. M., Brady, A. F., Burrows, N. P., Castori, M., Cohen, H., Colombi, M., Demirdas, S., De Backer, J., De Paepe, A., Fournel-Gigleux, S., Frank, M., Ghali, N., … Tinkle, B. (2017). The 2017 international classification of the Ehlers-Danlos syndromes. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *175*(1), 8–26. https://doi.org/10.1002/ajmg.c.31552

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

O'Connor, S. R., Tully, M. A., Ryan, B., Bradley, J. M., Baxter, G. D., & McDonough, S. M. (2015). Failure of a numerical quality assessment scale to identify potential risk of bias in a systematic review: A comparison study. *BMC Research Notes*, *8*, 224. https://doi.org/10.1186/s13104-015-1181-1

Pacey, V., Tofts, L., Adams, R. D., Munns, C. F., & Nicholson, L. L. (2013). Exercise in children with joint hypermobility syndrome and knee pain: A randomised controlled trial comparing exercise into hypermobile versus neutral knee extension. *Pediatric Rheumatology Online Journal*, *11*(1), 30. https://doi.org/10.1186/1546-0096-11-30

Peterson, B., Coda, A., Pacey, V., & Hawke, F. (2018). Physical and mechanical therapies for lower limb symptoms in children with hypermobility spectrum disorder and hypermobile Ehlers-Danlos syndrome: A systematic review. *Journal of Foot and Ankle Research*, *11*, 59. https://doi.org/10.1186/s13047-018-0302-1

Revivo, G., Amstutz, D. K., Gagnon, C. M., & McCormick, Z. L. (2019). Interdisciplinary pain management improves pain and function in pediatric patients with chronic pain associated with joint hypermobility syndrome. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *11*(2), 150–157. https://doi.org/10.1016/j.pmrj.2018.06.018

Reychler, G., Liistro, G., Pierard, G. E., Hermanns-Le, T., & Manicourt, D. (2019). Inspiratory muscle strength training improves lung function in patients with the hypermobile Ehlers-Danlos syndrome: A randomized controlled trial. *American Journal of Medical Genetics. Part A*, *179*(3), 356–364. https://doi.org/10.1002/ajmg.a.61016

Robbins, S. M., Cossette-Levasseur, M., Kikuchi, K., Sarjeant, J., Shiu, Y. G., Azar, C., & Hazel, E. M. (2020). Neuromuscular activation differences during gait in patients with Ehlers-Danlos syndrome and healthy adults. *Arthritis Care & Research (Hoboken)*, *72*(11), 1653–1662. https://doi.org/10.1002/acr.24067

Rombaut, L., Malfait, F., Cools, A., De Paepe, A., & Calders, P. (2010). Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. *Disability and Rehabilitation*, *32*(16), 1339–1345. https://doi.org/10.3109/09638280903514739

Rombaut, L., Malfait, F., De Wandele, I., Cools, A., Thijs, Y., De Paepe, A., & Calders, P. (2011). Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. *Archives of Physical Medicine and Rehabilitation*, *92*(7), 1106–1112. https://doi.org/10.1016/j.apmr.2011.01.016

Rombaut, L., Malfait, F., De Wandele, I., Taes, Y., Thijs, Y., De Paepe, A., & Calders, P. (2012). Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers-Danlos syndrome. *Arthritis Care & Research (Hoboken)*, *64*(10), 1584–1592. https://doi.org/10.1002/acr.21726

Sahin, N., Baskent, A., Cakmak, A., Salli, A., Ugurlu, H., & Berker, E. (2008). Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. *Rheumatology International*, *28*(10), 995–1000. https://doi.org/10.1007/s00296-008-0566-z

Scheper, M., Rombaut, L., de Vries, J., De Wandele, I., van der Esch, M., Visser, B., Malfait, F., Calders, P., & Engelbert, R. (2017). The association between muscle strength and activity limitations in patients with the hypermobility type of Ehlers-Danlos syndrome: The impact of proprioception. *Disability and Rehabilitation*, *39*(14), 1391–1397. https://doi.org/10.1080/09638288.2016.1196396

Shibata, S., Fu, Q., Bivens, T. B., Hastings, J. L., Wang, W., & Levine, B. D. (2012). Short-term exercise training improves the cardiovascular response to exercise in the postural orthostatic tachycardia syndrome. *The Journal of Physiology*, *590*(15), 3495–3505. https://doi.org/10.1113/jphysiol.2012.233858

To, M., & Alexander, C. M. (2019). Are people with joint hypermobility syndrome slow to strengthen? *Archives of Physical Medicine and Rehabilitation*, *100*(7), 1243–1250. https://doi.org/10.1016/j.apmr.2018.11.021

Toprak Celenay, S., & Ozer Kaya, D. (2017). Effects of spinal stabilization exercises in women with benign joint hypermobility syndrome: A randomized controlled trial. *Rheumatology International*, *37*(9), 1461–1468. https://doi.org/10.1007/s00296-017-3713-6

Voermans, N. C., Knoop, H., Bleijenberg, G., & van Engelen, B. G. (2010). Pain in ehlers-danlos syndrome is common, severe, and associated with functional impairment. *Journal of Pain and Symptom Management*, *40*(3), 370–378. https://doi.org/10.1016/j.jpainsymman.2009.12.026

Voermans, N. C., Knoop, H., Bleijenberg, G., & van Engelen, B. G. (2011). Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: An explorative study. *Physiotherapy*, *97*(2), 170–174. https://doi.org/10.1016/j.physio.2010.06.001

Wallman, D., Weinberg, J., & Hohler, A. D. (2014). Ehlers-Danlos syndrome and postural tachycardia syndrome: A relationship study. *Journal of the Neurological Sciences*, *340*(1–2), 99–102. https://doi.org/10.1016/j.jns.2014.03.002

Zeitoun, J. D., Lefevre, J. H., de Parades, V., Sejourne, C., Sobhani, I., Coffin, B., & Hamonet, C. (2013). Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: Results of a national cohort study on 134 patients. *PLoS One*, *8*(11), e80321. https://doi.org/10.1371/journal.pone.0080321

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