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The association between muscle strength and activity limitations in patients with the hypermobility type of Ehlers–Danlos syndrome: the impact of proprioception

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ABSTRACT

Purpose: The patients diagnosed with Ehlers–Danlos Syndrome Hypermobility Type (EDS-HT) are characterized by pain, proprioceptive inacuity, muscle weakness, potentially leading to activity limitations. In EDS-HT, a direct relationship between muscle strength, proprioception and activity limitations has never been studied. The objective of the study was to establish the association between muscle strength and activity limitations and the impact of proprioception on this association in EDS-HT patients.

Methods: Twenty-four EDS-HT patients were compared with 24 controls. Activity limitations were quantified by Health Assessment Questionnaire (HAQ), Six-Minute Walk test (6MWT) and 30-s chair-rise test (30CRT). Muscle strength was quantified by handheld dynamometry. Proprioception was quantified by movement detection paradigm. In analyses, the association between muscle strength and activity limitations was controlled for proprioception and confounders.

Results: Muscle strength was associated with 30CRT ($r = 0.67$, $p = <0.001$), 6MWT ($r = 0.58$, $p = <0.001$) and HAQ ($r = 0.63$, $p = <0.001$). Proprioception was associated with 30CRT ($r = 0.55$, $p < 0.001$), 6MWT ($r = 0.40$, $p = <0.05$) and HAQ ($r = 0.46$, $p < 0.05$). Muscle strength was found to be associated with activity limitations, however, proprioceptive inacuity confounded this association.

Conclusions: Muscle strength is associated with activity limitations in EDS-HT patients. Joint proprioception is of influence on this association and should be considered in the development of new treatment strategies for patients with EDS-HT.

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Activity limitations; Ehlers–Danlos (hypermobility type); muscle strength; musculoskeletal complaints; proprioception

➤ IMPLICATIONS FOR REHABILITATION

- Reducing activity limitations by enhancing muscle strength is frequently applied in the treatment of EDS-HT patients. Although evidence regarding treatment efficacy is scarce, the current paper confirms the rationality that muscle strength is an important factor in the occurrence of activity limitations in EDS-HT patients.
- Although muscle strength is the most dominant factor that is associated with activity limitations, this association is confounded by proprioception. In contrast to common belief proprioception was not directly associated with activity limitations but confounded this association. Controlling muscle strength on the bases of proprioceptive input may be more important for reducing activity limitations than just enhancing sheer muscle strength.

Introduction

Patients diagnosed with Ehlers–Danlos syndrome, are characterized by an altered structural integrity of connective tissue [1,2] resulting in frailty [3] and multi-systemic manifestations like orthostatic intolerance,[4] hyper-elastic skin,[5] organ dysfunction [6] and joint instability.[7] The phenotype of EDS-HT is heterogeneous, in which the severity of complaints varies from mild to severe.[5,8] Despite of this, a specific clinical pattern is present on which the diagnosis is established.[8] Clinical diagnosis of EDS-HT is based on the Villefranche criteria, a validated set of clinical features, that are specific to EDS-HT, in which the presence of Generalized Joint Hypermobility (GJH), hyper-elastic skin, pain, form the mainstay of diagnostic criteria.[8–10]

Pain and fatigue are highly prevalent in EDS-HT patients. Pain is present in multiple joints over a period of >3 months is one of the diagnostic criteria.[9] Pain has several causes and can appear by minimal provocation and is frequently the result of biomechanical overload. Pain and fatigue,[10,11] combined with multi-systemic dysfunction, may cause severe limitations in daily activities. [12,13] EDS-HT patients often perceive limitations during (stair) walking, self-care, transfers, sports and household activities.[12] In addition, these individuals show an higher dependency on assistive devices.[14] The underlying mechanisms of the musculoskeletal complaints and functional decline remain unknown.[15]

In EDS-HT patients, an important aim of rehabilitation is to reduce activity limitations by increasing muscle strength and

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enhancing motor control. However, the evidence to support this rationality is scarce.[10,15–17] When developing effective treatment it is essential to know which factors are associated with activity limitations. Muscle strength might be an important determinant of activity limitations, however, a direct relationship between muscle strength and activity limitations in EDS-HT has never been demonstrated. Muscle weakness and atrophy have frequently been observed in both non-symptomatic [18] (e.g. dancers) and symptomatic forms of GJH (e.g. EDS-HT, hypermobility syndrome) [19–21] In these studies, muscle weakness was found to be associated with pain [22] and fatigue.[21] However, whether these factors moderate the association between muscle strength and activity limitations is unknown. The association between activity limitations and muscle strength might also be influenced by biomechanical factors, such as joint proprioception. Proprioception provides the brain with positional and motion sense through mechanoreceptors localized within joint-capsules, muscles and tendons. Neural inputs derived from proprioceptive sensors are hypothesized to be crucial for the recruitment of motor units in relation to task requirements. [23] It has been shown that proprioception of the knee is reduced in EDS-HT patients,[24,25] however, the impact of proprioception on the association between muscle strength and activity limitations in EDS-HT is unknown.

Therefore, the aim of the study was to establish the association between muscle strength and activity limitations controlled for proprioception, pain and fatigue in EDS-HT patients.

Patients and methods

Participants

Twenty-four EDS-HT patients were recruited from the Center for Medical Genetics at the Ghent University Hospital (Table 1). Inclusion was based on the Villefranche criteria:[9] GJH present (Beighton score $\geq$5/9), skin hyper-extensibility, in combination with recurring joint dislocations, pain lasting for >3 months and a positive family history. As more than 90% of the EDS-HT participants is female,[9] the current study included only women. In addition, 24 female healthy volunteers participated. Exclusion criteria for the control subjects were: (1) a Beighton score <4/9,[18] (2) any musculoskeletal pain at present, and (3) the use of analgesics or antidepressants. Written informed consent was obtained from all the participants according to the Helsinki Declaration. The study was approved by the Medical Ethics Board of Ghent University Hospital.

Height(m) and weight(kg) were measured standardized and Body Mass Index (BMI: kg/m^2) was calculated. Skin-laxity was determined by suction cup method [5] and expressed in retraction force (*VE*: kg/cm^2). Joint hypermobility was determined by the Beighton score.[26] Disease severity, time since diagnosis, painful body surface(%), type of complaints, medication and comorbidity, were obtained by structured interview.

Outcome measurements

Activity limitations

Activity limitations were quantified in both capacity and performance qualifiers, according to the International Classification of Functioning (ICF).[27,28] At the level of capacity,[29] the 30s chair-rise test [30] (30CRT) and the six-minute walk test (6MWT) were used.[31] At the level of performance, the Health Assessment Questionnaire (HAQ) was used.[32]

The 30CRT was performed on a stationary chair without armrests with a standardized height of 47.5 cm.[30] The participants were instructed to rise from sitting position to complete stance, without using the arms, as often as possible in 30s. Each successful raise, defined as a complete rise from sit to stance was recorded with a lap counter. Two trial attempts were performed. No verbal encouragements were given.

The 6MWT was performed along an 8-m track in a straight.[31] Participants were instructed to cover the largest possible distance in six minutes at a self-chosen walking speed. Turns were made on both ends of the 8-m track. Patients were encouraged every minute in a standardized way. The outcome of the 6MWT was expressed in meters walked and used in analyses.

The HAQ contains 20 items measuring activity limitations over the past week in eight categories: self-care, rising, eating, walking, hygiene, reach, grip and activities.[32] Each item was scored on a 4-point scale from 0 (no difficulty) to 3 (unable). The overall score was calculated by summing and averaging the highest item score of each category.[33] In order to account for the usage of assistive devices, in agreement with standardized usage of the HAQ, a disability index was calculated and used for analysis.[33] The HAQ disability index ranges from 0 to 3, where scores of 0 –1 represent

Table 1. Clinical characteristics.

	EDS-HT		Controls		
	Mean (SD)	Range	Mean (SD)	Range	*p* Values
Age (years)	41 (11)	21–57	39 (10)	24–57	$p = 0.451$
BMI (Kg/cm^2)	**27.8 (4.7)**	**20.1–37.2**	**22.8 (2.9)**	**17.9–28.6**	**$p < 0.0001$**
Connective tissue laxity					
Generalized joint hypermobility (Beighton score $\geq$5)[c]	71%	($n = 17$)	–	–	–
Skin laxity (VE)[a]	**3.7**	**2.9–4.2**	**4.4**	**3.4–5.2**	**$p = 0.032$**
Activity Limitations					
30s chair rise (repetitions)	**10 (3)**	**3–18**	**16 (2)**	**12–21**	**$p < 0.0001$**
6MWT (m)	**358 (133)**	**101–525**	**579 (78)**	**462–762**	**$p < 0.0001$**
HAQ (disability index: 0–3)	**1.30 (.52)**	**0.4–2.3**	**0.04 (0.14)**	**0.0–0.63**	**$p < 0.0001$**
Musculoskeletal function					
Muscle strength (Normalized)[b]	**33.7 (7.0)**	**23.1–47.1**	**42.3 (6.4)**	**33.6–47.1**	**$p < 0.0001$**
Proprioception (angle of detection°)	**1.8 (1.5)**	**0.33–5.9**	**0.8 (0.4)**	**0.0–1.8**	**$p = 0.004$**
Disease status					
Time since diagnosis (years)	8 (8)	1–38	–	–	–
Total painful body surface (%)	29 (18)	4–64	–	–	–
Pain intensity (VAS, in mm)	65 (17)	16–95	–	–	–
Fatigue (CIS20 score)	62 (18)	20–98	–	–	–

Statistical significant differences are highlighted in bold.
[a]Median score and interquartile range (P25–P75).
[b]Normalised over fat-free body mass.
[c]Percentage of subject classified with GJH.

mild to moderate disability, 1–2 moderate to severe disability, and 2–3 severe to very severe disability.[33]

Musculoskeletal function

Muscle strength in both extremities was measured bilaterally in a standardized way [19] with a hand-held dynamometer (Citec, Groningen, The Netherlands). Measurements were consecutively performed three times and the highest value was registered. In the upper extremity, shoulder abductor and grip strength were measured. In the lower extremity, hip flexors, knee extensors and ankle extensors were measured. All measurements were performed according to the ``break method'' with the exception of the knee extension and grip strength. For these measurements the ``make method'' was applied due to the inability of the assessors to break the generated force of the participant.[34] Total muscle strength was calculated by a summation of all muscles (left and right) and normalized over fat-free body mass which was ascertained by bio-impedance testing.[35] Normalized muscle strength was used for the analysis (Newtons/fat-free mass).

Knee proprioception was measured according to the protocol of Hurkmans et al.[36] This protocol has been used in healthy adults and in osteoarthritis patients and demonstrated high inter- and intra-reliability.[36] The device consists of a chair with a computer-controlled motor system and two attached free-moving arms. Each arm supports the subjects shank and foot and moves in the sagittal plane. The joint of each arm is moved by a computer-controlled motor and transmission system for angular displacement. The ankle is attached with an air splint to the footrest. The measurement procedure consisted of a movement detection task. Each trial, the leg was moved to a starting position of 30° knee flexion. Upon reaching this position, movement was stopped. Following a random delay, the knee extended further with an angular velocity of 0.3°/s. Participants were instructed to push a button at the moment of definite detection. The angular displacement between the starting position at 30° flexion and the position in the extension direction at the instance when the button is pushed was recorded in degrees as the measure of knee joint proprioception. Measures were taken to ensure that the movement of the legs was mainly detected by proprioceptive senses and not by visual, auditory, vibrational or skin compression ques.[36] The angle of movement detection, expressed in degrees, was used for the analyses.

Pain and fatigue

Pain was measured with the Visual Analog Scale (VAS) expressed in mm, ranging from no pain (score: 0 mm) to worst pain (score: 100 mm). Subjects rated the average pain in the previous two weeks.

Fatigue, perceived in the previous two weeks, was measured by the Checklist Individual Strength (CIS). The CIS measures four dimensions of fatigue: the subjective perception, motivation, activity, and concentration. The CIS was reported to be reliable and valid in healthy controls and other chronic diseases.[37] The total CIS score was calculated through summation of all the sub-items resulting in a score ranging from 0 to 100, (no fatigue to 100 as worst fatigue) and used for the analyses.[37]

Statistical analysis

First, descriptions of all outcomes and measures of central tendency were calculated. All outcomes were centered by *z*-score transformation in order to prevent collinearity. Healthy matched controls were used within the statistical analysis as a contrast group in order to demonstrate the divergence from normality. Differences between the subjects were determined by independent Student *t*-test.

Second, the associations between dependent (activity limitations) and independent variables (muscle strength, proprioception, pain, fatigue) were estimated by Pearsons correlation coefficients.

Finally, mixed linear models were constructed for each outcome of activity limitations. A two-level (patient/controls) structure was used with activity limitations as the dependent and muscle strength, proprioception the independent variables. First the association between the activity limitations and muscle strength was determined (initial model). Second, proprioception was added to the model. In the final step the association between muscle strength and activity limitations was adjusted for pain, fatigue, age, BMI and time since diagnosis.

In the adjusted models all independent variables were entered stepwise. Results are presented in unstandardized regression coefficients (Beta) and standard errors (SE) with 95% confidence intervals (95%CI). All the statistical analyses were performed in SPSS version 22.0. p Values $<$ (0).05 were considered statistically significant.

Results

Descriptives

The mean age of the population was 40 years (SD: 10, range: 21–57). In EDS-HT patients ($n = 24$), duration of pain in years (mean (SD)) was 24(12) and the duration of soft tissue injuries (mean years (SD)) was 23(13). Fatigue was present in 92% of the EDS-HT patients (mean years (SD): 14(11). Gastro-intestinal complaints were present in 80% of the EDS-HT patients (mean years (SD): 14 (14). Time since diagnosis (mean years (SD) was 8.2(7.8). All included EDS-HT patients fulfilled the Ville-Franche criteria ($n = 24$: 100%) and thus the diagnosis of EDS-HT was confirmed. When regarding the main diagnostic criteria: GJH (Beighton $\geq$5) was present in 17 subjects (71%), Hyper-elastic skin was present in all the subjects ($n = 24$: 100%). When regarding the minor criteria: in all subjects recurring joint dislocations and chronic pain (>3 months) were present ($n = 24$: 100%) and in 10 subjects a positive family history was present (42%).

Differences between EDS-HT patients and controls were observed. EDS-HT patients showed significant higher skin laxity (ΔD: +15.9%, $p = 0.032$), higher BMI (ΔD: +16.5%, $p<0.0001$), lower muscle strength (ΔD: −20.2%, $p<0.0001$) and poorer proprioception, in terms of higher errors in movement detection (ΔD: 43.6%, $p = 0.004$). EDS-HT patients showed a significant lower score on 30CRT (ΔD: −59.9%, $p < 0.0001$), on 6MWT (ΔD: −61.8%, $p < 0.001$) and higher HAQ disability indexes (ΔD: +97.9%, $p < 0.001$).

Table 2. Correlation matrix: Pearsons correlation coefficients (*r*).

Activity limitations (dependent)	Muscle strength	Proprioception	Pain	Fatigue
30CRT	+0.67*	−0.56**	−0.65**	−0.47**
6MWT	+0.58**	−0.41*	−0.70**	−0.47**
HAQ	−0.63**	+0.46*	+0.80**	+0.65**
Muscle strength		−0.58**	−0.57**	−0.48**
Proprioception	−0.58**		+0.42*	+0.33*
Pain	−0.57**	+0.42*		+0.62**
Fatigue	−0.48**	+0.33*	+0.62**	

*$p = <0.05$.
**Fatigue $p = <0.0001$.

Table 3. Multivariate analysis (random effects model) concerning muscle strength and 30CRT.

30CRT					
	B (SE)	95% CI		*p* Values	Goodness of fit
Stage 1: initial model (unadjusted)					
Muscle strength	0.39 (0.10)	0.19	0.59	<0.0001	AICC: 101.48
Stage 2: proprioception (adjusted)					
Muscle strength	0.27 (0.11)	0.05	0.49	0.017	AICC: 99.45
Proprioception	−0.23 (0.10)	−0.44	−0.02	0.034	
Stage 3: Confounders (backward selection)					
Muscle strength	0.26 (0.11)	0.03	0.49	0.025	AICC: 97.89
Proprioception	−0.20 (0.11)	−0.43	−0.01	0.040	
Pain	−0.12 (0.14)	−0.20	0.16	0.199	

Table 4. Multivariate analysis (random effects model) concerning muscle strength and 6MWT.

6MWT					
	B (SE)	95% CI		*p* Values	Goodness of fit
Stage 1: initial model (unadjusted)					
Muscle strength	0.28 (0.12)	0.03	0.52	0.028	AICC: 122.09
Stage 2: proprioception (adjusted)					
Muscle strength	0.27 (0.14)	−0.01	0.58	0.053	AICC: 124.00
Proprioception	−0.02 (0.14)	−0.26	0.29	0.756	
Stage 3: Confounders (backward selection)					
Muscle strength	0.29 (0.14)	0.03	0.57	0.033	AICC: 116.74
Proprioception	0.14 (0.13)	−0.12	0.41	0.286	
Age	−0.24 (0.11)	−0.47	−0.02	0.023	
Pain	−0.63 (0.12)	−0.88	−0.39	<0.0001	

Univariate analysis: correlations

Table 2 presents the correlations between activity limitations (30CRT, 6MWT, HAQ), muscle strength and knee joint proprioception.

Low muscle strength, was correlated with low scores on 30CRT ($r = 0.67$, $p < 0.0001$), 6MWT ($r = 0.587$, $p < 0.0001$) and higher HAQ scores ($r = -0.63$, $p < 0.0001$). Poor proprioception was correlated with low scores on 30CRT ($r = -0.56$, $p < 0.0001$), 6MWT ($r = -0.41$, $p < 0.05$) and high HAQ scores ($r = 0.46$, $p < 0.05$).

Low muscle strength was correlated with poor proprioception ($r = -0.58$, $p < 0.0001$) pain ($r = -0.57$, $p = <0.0001$) and fatigue ($r = -0.48$, $p = <0.0001$).

Multivariate analysis

Multivariate analyses are presented in Tables 3, 4, and 5 for each outcome of activity limitation separately.

30CRT

The results of the random effects model concerning activity limitations, in terms of 30CRT, are depicted in Table 3. In the initial model (AICC: 101.48) muscle strength was associated with increased 30CRT scores (*B*(SE): 0.39 (0.10), $p = <0.0001$). In the adjusted model (AICC: 100.26), proprioception was associated with lower scores on 30CRT (*B*(SE): −0.23 (0.11), $p = 0.034$). Proprioception changed the Beta of muscle strength with >10% and confounded the association between muscle strength and 30CRT (*B*(SE): 0.27 (0.11), $p = 0.017$). In the final step (AICC: 97.89), when controlling for confounders, muscle strength remained associated with activity limitations (*B*(SE): 0.26 (0.10), $p = 0.007$) as did proprioception (*B*(SE): 0.27(0.10), $p = 0.028$). Pain reached the retention threshold but was not significantly associated with activity limitations according to the 30CRT (*B*(SE): −0.07 (0.13), $p = 0.199$) and did not change the Beta of muscle strength with >10%.

Table 5. Multivariate analysis (random effects model) concerning muscle strength and HAQ.

HAQ					
	B (SE)	95% CI		*p* Values	Goodness of fit
Stage 1: initial model (unadjusted)					
Muscle strength	−0.38 (0.10)	−0.59	−0.18	<0.0001	AICC: 103.76
Stage 2: proprioception (adjusted)					
Muscle strength	−0.24 (0.11)	−0.46	−0.02	0.034	AICC: 100.35
Proprioception	0.27 (0.10)	0.05	0.47	0.016	
Stage 3: Confounders (backward selection)					
Muscle strength	−0.20 (0.11)	−0.42	−0.02	0.049	AICC: 99.17
Proprioception	0.24 (0.10)	0.04	0.45	0.021	
Pain	0.38 (0.13)	0.12	0.66	0.006	
Fatigue	0.25 (0.08)	0.09	0.41	0.003	

6MWT

The results of the random effects model concerning activity limitations, in terms of 6MWT, are depicted in Table 4. In the unadjusted model (AICC: 122.09), muscle strength was associated with the 6MWT (*B*(SE): 0.28 (0.12), $p = 0.028$). The adjusted model (AICC: 124.00) showed that proprioception did not contribute to activity limitations, according to 6MWT (*B*(SE): −0.02 (0.13), $p = 0.756$) and did not change the Beta of muscle strength with->10%. Proprioception did not confound the association between muscle strength and 6MWT (*B*(SE): 0.27 (0.14), $p > 0.200$). In the final step (AICC: 116.39), when controlling for confounders, muscle strength remained significantly associated with activity limitations (*B*(SE): 0.29 (0.13), $p = 0.033$) as did pain (*B*(SE): −0.63 (0.12), $p = <0.0001$) and age (*B*(SE): −0.24 (0.11), $p = 0.031$). No other factors were found to be significant nor were retained ($p = >0.200$). The addition of pain and age to the model with muscle strength and proprioception did not result in a change in the Beta of muscle strength >10%.

HAQ

The results of the random effects model concerning activity limitations, in terms of HAQ, are depicted in Table 5. In the initial model (AICC: 103.76), muscle strength was associated with HAQ (*B*(SE): 0.38 (0.10), $p = <0.0001$). In the adjusted model (AICC: 100.35), proprioception was found to be associated with higher activity limitations according to HAQ (*B*(SE): 0.27 (0.10), $p = 0.016$). Proprioception (*B*(SE): −0.24 (0.11), $p = 0.034$) did change the Beta of muscle strength with >10%. When controlling for confounders (AICC: 99.17), muscle strength remained associated with the HAQ (*B*(SE): −0.20 (0.10), $p = 0.049$) as was proprioception (*B*(SE): 0.24 (0.12), $p = 0.021$). Pain (*B*(SE): 0.38 (0.13), $p = 0.006$) and fatigue (*B*(SE): 0.25 (0.08), $p = 0.003$) were also found to be associated with higher disability, and did change the Beta of muscle strength with >10%.

Discussion

Muscle strength was found to be associated with activity limitations in EDS-HT patients. This finding is important, despite the prevalent use of muscle strength enhancement in clinical practice aiming at reducing activity limitations, the scientific ground for such rationale is lacking.[15] Proprioception confounded the association between muscle strength and the HAQ and the 30CRT, but not the association between muscle strength and 6 MWT. These results indicate that proprioception is of influence on the

associations between muscle strength and activity limitations, but this influence is not consistent. These findings support evidence for the core assumption that treatment based on muscle strengthening and increasing proprioception acuity might be effective [38] in patients with EDS-HT. Although the present study provides supporting evidence for the usage of muscle strength training as a treatment modality, it also raises questions that should be addressed before strength training can be implemented into practice

Muscle strength in EDS-HT patients was lower than healthy controls. The difference in muscle strength can be explained by the difference in connective tissue, the main clinical characteristic of EDS-HT patients. In these patients more elastic and potentially more fragile connective tissue is present, which is expressed in GJH and a hyper-extensible skin. Previous research has shown that the presence of GJH is an independent factor associated with muscle weakness, not only in subjects with symptomatic forms of GJH but also in healthy professional dancers.[18] It can be hypothesized that muscle weakness is not only the result of deconditioning, but is partially caused by the inefficient force transfer through muscle fibers due to altered structural integrity of connective tissue.[39] If this hypothesis is true, it could have consequences for the trainability of muscle strength in EDS-HT patients. As connective tissue stiffness cannot be influenced, the effect of muscle strength training may be limited. However, these findings were reported [18] in adolescents and young adults which were more flexible compared to the currently included population. The only influence on tissue stiffness is aging. Joint mobility decreases over time as a result of aging [40] and could also reduce the influence of connective tissue laxity on muscle strength.

We found that poor proprioception is associated with an increase in activity limitations. Poor proprioception has frequently been reported in EDS-HT patients and has been postulated to be an important factor in activity limitations.[17,24,41] Our results indicate that poor proprioception, especially during activities that require controlling discrete joint motion (knee flexion), has an influence on muscle strength. However, the generalizability to other joints within the functional chain is unknown. Other activities like walking are less dependent on knee flexion and therefore proprioception measured at the knee could not be as important for walking as it is for rising to stance which is marked as a limitation of the study. It has been shown that the function of proprioception is not limited to providing the brain with coordinates of joint positions, but also plays an important role in the coordination of muscle force in relation to the required movements.[23] Our results might indicate that proprioception is especially important for coordinating muscle force rather than controlling joint angular momentum. Transferring these results into clinical practice, it can be speculated that learning to control the required muscle force is more important than just increasing raw muscle power. Possible reasons for poor proprioception are part of discussion. One possible reason is that proprioceptive signals are based on inadequate mechanical forces generated from lax joint-capsules and muscle tissue.[42] In EDS-HT patients this would result in an increased activation threshold, due to altered mechanical properties of connective tissue, and resulting in decreased proprioceptive feedback. Another possible reason could be muscle atrophy. Muscle atrophy has been found to result in a reduction of proprioceptive sensor density in osteoarthritis patients. Although a reduced sensor density has not been demonstrated in EDS-HT, the presence of muscle atrophy has indeed been shown in EDS-HT patients.[20] Therefore, the prevention of muscle atrophy by muscle training could also protect against poor proprioception. If connective tissue laxity and muscle atrophy are responsible for poor proprioception, for reasons of parsimony, this should be studied in longitudinal studies first before implementing in clinical practice.

Pain and fatigue were found to be independently associated with activity limitations. It is postulated that the origin of pain in EDS-HT patients can be found in micro-fractures within joint surfaces [41] and muscle structures [15] which leads to activity limitations and in turn to further muscle weakness.[10] Overuse could potentially activate nociceptive receptors which could inhibit motor unit recruitment and further add to muscle weakness.[43] In addition, pain and poor proprioception were also found to be correlated. However, in multi-regression analysis, pain did not influence the associations between activity limitations, muscle strength and proprioception. Statistical testing did not show any indications for multi-collinearity in terms of: univariate correlations did not exceed >0.80, tolerances were >0.5 and the Variance Inflation Factor (VIF) ranged from 1.6 to 2.0.[44] In combination with the usage of centering the presence of multi-collinearity can be excluded in all models. However, EDS-HT patients were found to have lower pain thresholds which could also be a factor that may lead to activity avoidance. The presence of secondary hyperalgesia and proprioceptive inacuity could also indicate neurologically oriented mechanism that affects sensory modalities.[45] Regarding fatigue, muscle weakness could result in additional effort during functional activities which may in turn lead to inefficient energy consumption.

In order to correctly interpret these results, the following limitations should be considered. First, the study is of cross-sectional nature and thus no causative conclusions can be drawn nor does it show that strength training is an effective treatment. These results do support exploratory evidence that muscle strength is a relevant factor in the development of activity limitations in patients with EDS-HT. Second, EDS-HT is more frequently present in females, therefore, only females were included in the study. Our observations might be different in males. Finally, data on psychological functioning were not incorporated in the models due to small sample size. When considering the high prevalence of psychological comorbidity, like anxiety, these could also have considerable effects on activity limitations.

Conclusion

Muscle strength is associated with activity limitations in EDS-HT patients. Proprioception is of influence on this association and should be considered in the development of treatment strategies aiming to reduce activity limitation in EDS-HT patients.

Disclosure statement

The authors confirm to have no conflicts of interest or any financial disclosures and that all of contributors participated in the research and in finalizing the paper for publication

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