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ORIGINAL ARTICLE

# Muscle Mass, Muscle Strength, Functional Performance, and Physical Impairment in Women With the Hypermobility Type of Ehlers-Danlos Syndrome

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***Objective.*** **To investigate lower extremity muscle mass, muscle strength, functional performance, and physical impairment in women with the Ehlers-Danlos syndrome hypermobility type (EDS-HT).**

***Methods.*** **Forty-three women with EDS-HT and 43 sex- and age-matched healthy control subjects participated. Muscle mass was determined by dual x-ray absorptiometry. Muscle strength and muscle strength endurance were measured with isokinetic dynamometry at angular velocities of 60, 180, and 240°/second. Static muscle endurance during posture maintenance was also assessed. Pain and fatigue were simultaneously evaluated by visual analog scale and the Borg scale, respectively. In addition, the chair rise test for assessment of functional performance and the Arthritis Impact Measurement Scales (AIMS) for physical impairment evaluation were used.**

***Results.*** **Compared to control subjects, EDS-HT patients showed substantial lower extremity muscle weakness, reflected by significantly reduced knee extensor and flexor muscle strength and endurance parameters, with differences ranging from −30% to −49%; reduced static muscle endurance time; and diminished functional performance. Lower extremity muscle mass was similar in both groups and unlikely to affect the muscle strength results. By contrast, pain and fatigue were omnipresent and increased remarkably due to the tests. Furthermore, the EDS-HT group was physically impaired, especially in the AIMS domain walking and bending.**

***Conclusion.*** **This study demonstrates severely reduced quantitative muscle function and impairment in physical function in patients with EDS-HT compared to age- and sex-matched controls. The muscle weakness may be due to muscle dysfunction rather than reduced muscle mass. Whether muscle strength and endurance can be improved by appropriate exercise programs needs evaluation in further studies.**

## INTRODUCTION

Ehlers-Danlos syndrome (EDS) comprises a clinically and genetically heterogeneous group of inherited connective tissue disorders, of which the principal clinical features are skin laxity, tissue fragility, and joint hypermobility (1–3). The current classification, formalized in the Villefranche nosology, proposes 6 subtypes based on clinical, biochemical, and molecular characteristics (4). However, overlapping forms, unclassified variants, and several new subtypes, including the tenascin-X (TN-X)–deficient type of EDS, have been identified over the last decade (5). Most EDS subtypes are caused by mutations in genes encoding fibrillar collagens type I, III, or V or collagen-modifying enzymes. However, the genetic background of the hypermobility type of EDS (EDS-HT), which is by far the most common type, remains poorly defined at present (5). Diagnosis is consequently based on clinical criteria, including generalized severe joint hypermobility, recurrent joint dislocations, debilitating chronic pain, and mild skin involvement (4). Although not defined in the diagnostic criteria for EDS-HT, muscular involvement, such as muscle weakness, muscle pain, muscle cramps, and muscle ruptures, has been suggested to be a common associated feature in these patients (6,7).

Muscle symptoms in EDS have long been considered to result from reduced physical activity (PA), which may

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## Significance & Innovations

- Patients with Ehlers-Danlos syndrome hypermobility type (EDS-HT) show considerably reduced lower extremity muscle strength and muscle strength endurance, which is reflected in a poorer functional performance.
- The muscle weakness may be due to muscle dysfunction rather than reduced muscle mass.
- Exercise-induced pain and fatigue in patients with EDS-HT increase disproportionately compared to the muscle performance, and remain extremely high and long-lasting after the effort.
- Patients with EDS-HT show important impairments in physical function, particularly in activities such as walking and bending.

occur as a consequence of exercise avoidance due to joint hypermobility, joint instability, and pain. However, recent studies have shown that primary muscle involvement in EDS can be expected based on altered interactions between muscle cells and extracellular matrix (ECM) molecules, of which collagen is an important component (8–10). Despite this growing evidence for muscular involvement in EDS, muscle function in EDS, and specifically in the hypermobility type, has hardly been investigated. One study by Voermans et al (10) demonstrated mild to moderate muscle weakness, myalgia, hypotonia, and some myopathic features in the vascular, classic, and TN-X–deficient EDS types, and to a lesser extent, in patients with EDS-HT caused by TN-XB gene haploinsufficiency (n = 10). However, haploinsufficiency of TN-X has been identified only in a minority (5%) of patients with EDS-HT (11). Therefore, quantitative muscle function evaluation is still lacking in a substantial group of patients diagnosed with EDS-HT.

Nevertheless, investigation of muscle performance in EDS-HT is particularly important to gain a better understanding of how and to what extent muscle function is impaired in EDS-HT. This knowledge may contribute to better management for these patients, which is currently poorly addressed (12,13). In addition, it has been shown that muscle weakness contributes to physical impairment in many disorders, e.g., rheumatoid arthritis (14) and fibromyalgia (15), which are both chronic musculoskeletal disorders displaying some clinical similarities to EDS-HT (7). More specifically, knee extensor muscle strength has been suggested to play a key role during several ambulatory and functional activities (16,17).

Therefore, we performed an extensive clinical study on lower extremity muscle function in EDS-HT. The primary objective was to investigate quadriceps and hamstrings muscle strength, strength endurance, functional performance, and muscle mass, as well as pain and fatigue associated with muscle strength tests, in patients with EDS-HT compared to healthy matched control subjects. The secondary objective was to examine the extent of physical impairment in patients with EDS-HT.

## SUBJECTS AND METHODS

**Subjects.** The study protocol was reviewed and approved by the Ethical Committee of Ghent University Hospital, and written informed consent was obtained from all of the participants. Since more than 90% of patients with EDS-HT are women (4), the current study included only women. In total, 86 white subjects participated, of whom 43 patients were diagnosed with EDS-HT and 43 were healthy control subjects. Patient selection was performed in the Centre for Medical Genetics at Ghent University Hospital on the basis of the Villefranche criteria for EDS-HT, which include the presence of generalized joint hypermobility (Beighton score of >4 of 9) (Table 1) and/or skin hyperextensibility/fragility, in combination with recurring joint dislocations, and/or chronic musculoskeletal pain, and/or a positive family history. Patients were excluded if they had a musculoskeletal injury at the lower extremity or had undergone knee surgery within the last 2 years. The control subjects were healthy volunteers individually matched for sex, age, and ethnicity. Exclusion criteria for the control subjects were a Beighton score of >4 of 9, surgery at the lower extremity or a severe knee or hip trauma in the past, any musculoskeletal injury at the lower extremity within the last 2 years, current lower extremity pain, and participation in competitive sports.

**Procedure.** All of the subjects were asked to refrain from strenuous exercise for 48 hours prior to the measurements. Subject characteristics, including age, height, weight, body mass index (BMI), Beighton score, and PA level, were collected (Table 1). PA level was assessed by the Baecke questionnaire (18), which quantifies work, sports, and leisure activities using a 5-point scale ranging from never to always. The sum of the 3 items is an indicator of habitual PA, with higher scores indicating a higher PA level. Each subject was then tested following a standard protocol in the order as described below.

**Measurements.** *Muscle strength.* Quadriceps and hamstrings strength of the dominant leg were assessed with a Biodex System 4 computerized isokinetic dynamometer (Biodex Medical Systems), which was calibrated before every test session. Leg dominance was determined by asking the subject which leg they would preferably kick a ball with. Subjects were positioned in an upright sitting position, with the thigh, pelvis, and trunk stabilized with fixation straps. The lever arm was attached to the subject's lower leg by a padded cuff 2 cm proximal to the medial malleolus, and the axis of rotation of the dynamometer arm coincided with the axis for knee flexion/extension. Maximal voluntary concentric knee flexion and extension movements were performed at the angular velocities of 60°/second and 180°/second for 5 repetitions each. The order of speed was from slower to faster, as suggested by Wilhite et al (19), and a 60-second rest period was provided between each angular velocity. Before each test, the subjects performed 3 consecutive submaximal warm-up trials to become familiar with the movement and velocity. All of the tests were conducted by the same researcher

**Table 1. Subjects' characteristics***

| | EDS-HT group | Control group | *P* |
|---|---|---|---|
| Age, years | 40 ± 10.8 | 40 ± 10.6 | 0.880 |
| Height, cm | 165 ± 7.4 | 168 ± 6.2 | 0.070 |
| Weight, kg | 69.8 ± 12.40 | 67.6 ± 10.98 | 0.378 |
| BMI, kg/m$^2$ | 25.8 ± 4.91 | 24.0 ± 3.59 | 0.059 |
| Beighton score (of total 9) | 6 ± 1.6 | 1 ± 1.2 | < 0.001† |
| Physical activity score | 6.4 ± 2.14 | 8.4 ± 1.28 | < 0.001† |
| Lean mass in dominant leg, kg | 7.2 ± 1.45 | 7.5 ± 1.21 | 0.289 |

* Values are the mean ± SD. EDS-HT = Ehlers-Danlos syndrome hypermobility type; BMI = body mass index.
† $P < 0.05$.

(LR), and the subjects were verbally encouraged to exert maximal efforts. In addition, the coefficient of variation (CV) was examined. The CV indicates how much variation occurred during the test between repetitions, or in more technical terms, the SD of the torque data divided by the mean torque. Large CVs can be attributed to underlying factors such as a lack of maximal effort. An acceptable CV for the quadriceps and hamstrings is ≤15% (20). Therefore, test results with a CV >15% were discarded and the test was repeated. This occurred only in a few subjects.

Peak torque (PT; Nm), PT/body weight (PT/BW; Nm/kg), and the hamstrings:quadriceps ratio (H:Q; percentage) were assessed for each velocity. PT is the highest absolute torque produced by the muscle and represents the muscle's maximum strength capability. PT/BW is the PT normalized for the subject's body weight, used to standardize and compare scores. The H:Q notes the balance between the PT of the knee flexors to knee extensors, which is of importance to dynamic stability of the knee joint. At the knee, an H:Q ratio of approximately 60% has been accepted as normal (21).

*Muscle strength endurance.* The same setup as described above was used to evaluate isokinetic muscle strength endurance, which was performed at an angular velocity of 240°/second across 30 maximal concentric contractions of knee extension and flexion. This is a modification of the test by Maquet et al (22), in that a higher velocity was used to decrease compressive forces on vulnerable joints in our EDS-HT population. The test was performed 60 seconds after the isokinetic test at 180°/second.

The parameters of interest were total work (J), work first third (J), work last third (J), and work fatigue (percentage). Total work is the work produced throughout the test and represents the muscle's capability. Work first third and work last third are the efforts produced during the first and last thirds of the test duration, respectively. Work fatigue is the percent decrease in torque output between the first third and the last third of work in the test. If a subject was not able to complete the entire test of 30 repetitions, the test was invalid and discarded from statistical analysis.

Then, after 10 minutes of rest, we evaluated muscle strength endurance in a static way by posture maintenance. The 2 postures examined were lying supine with 30° flexion of the dominant hip and standing with the back against the wall with 90° knee flexion, as described by Maquet et al (23). The length of time (seconds) a subject could maintain the given posture was determined. Time was started from the moment the subject adopted the correct position until the subject failed to maintain the posture. At least 5 minutes of rest were provided between each muscle strength endurance test.

*Pain and fatigue associated with muscle strength and endurance tests.* Pain severity of the lower extremity tested was evaluated just before and immediately after each muscle strength test and just before, immediately after, and 1 minute after each muscle strength endurance test. A visual analog scale (VAS; mm) was used, where a score of 0 indicates no pain and a score of 100 indicates unbearable pain. According to Jensen et al, 0–4 mm = no pain, 5–44 mm = mild pain, 45–74 mm = moderate pain, and 75–100 mm = severe pain (24).

In addition, fatigue was simultaneously evaluated just before, immediately after, and 1 minute after each muscle endurance test. The modified Borg scale was used, which is a simple method of rating perceived exertion with a 15-point scale (range 6–20) ranging from "not at all" to "very, very hard" exhausted (25).

*Muscle mass.* To examine the possibility that muscle atrophy is a basis for muscle weakness, lean tissue mass of the dominant lower extremity was obtained by total body dual x-ray absorptiometry (DXA; QDR 4500 DXA Discovery A device, Hologic). Appendicular lean mass (gm) was determined as muscle mass assuming that all nonfat and nonbone tissue was skeletal muscle. The lower extremity was defined as all tissue below a diagonal line drawn outward and upward from the groin area through the femoral neck. The measurement was performed by a well-trained and experienced nurse of the Department of Endocrinology at the Ghent University Hospital, and weekly whole-body phantom measurements showed CVs of <1%. This procedure has been validated against measurements with magnetic resonance imaging (26).

*Functional performance.* Functional lower extremity performance was evaluated by the chair rise test, which is a movement that is highly relevant in everyday life. A bench of 46 cm anchored to a Leonardo ground reaction force platform (Novotec Medical) was used. Starting by sitting on the bench with the feet on the ground and the arms folded across the chest, the subject was asked to stand up straight and to sit down instantly as quickly as possible 5 times. In the present study, total time and av-

**Table 2. Muscle strength***

| | EDS-HT group | Control group | Difference, % | *P* |
|---|---|---|---|---|
| Test at 60°/second | | | | |
| PT, Nm | | | | |
| Knee extensors | 84 ± 38.2 | 120 ± 26.1 | −30.0 | < 0.001† |
| Knee flexors | 44 ± 20.5 | 69 ± 12.8 | −36.2 | < 0.001† |
| PT/BW, Nm/kg | | | | |
| Knee extensors | 1.2 ± 0.52 | 1.8 ± 0.39 | −33.3 | < 0.001† |
| Knee flexors | 0.6 ± 0.26 | 1.0 ± 0.20 | −40.0 | < 0.001† |
| H:Q, % | 53 ± 14.1 | 58 ± 9.2 | | 0.115 |
| Test at 180°/second | | | | |
| PT, Nm | | | | |
| Knee extensors | 56 ± 26.9 | 79 ± 18.5 | −29.2 | < 0.001† |
| Knee flexors | 31 ± 16.2 | 46 ± 11.7 | −32.7 | < 0.001† |
| PT/BW, Nm/kg | | | | |
| Knee extensors | 0.8 ± 0.36 | 1.2 ± 0.26 | −33.3 | < 0.001† |
| Knee flexors | 0.4 ± 0.22 | 0.7 ± 0.18 | −42.9 | < 0.001† |
| H:Q, % | 54 ± 16.3 | 59 ± 10.8 | | 0.199 |

* Values are the mean ± SD unless otherwise indicated. EDS-HT = Ehlers-Danlos syndrome hypermobility type; difference = 100 × ([EDS-HT − control]/control); PT = peak torque; PT/BW = PT normalized for body weight; H:Q = PT hamstrings:PT quadriceps ratio.
† $P < 0.05$.

erage time per trial were obtained on the basis of vertical ground reaction forces exerted on the platform. If the average time per trial exceeded 2.5 seconds, the subject was regarded as having a substantial increased risk of falling and hip fracture. A score of <2.0 seconds has been accepted as normal (27).

*Physical impairment.* A validated Dutch version (for the northern part of Belgium) (28) and a French version (for the southern part of Belgium) (29) of the Arthritis Impact Measurement Scales (AIMS) were used to evaluate functional impairment by questionnaire. The AIMS was originally developed for rheumatoid arthritis but is now widely used in the field of rheumatology. Only the physical impairment dimension was of interest for the present study, comprising 28 items grouped into 6 subscales: mobility, walking and bending, hand and finger functions, arm functions, self-care, and household activities. For each subscale and for the overall physical dimension, a physical impairment score was calculated and graded from 0–10, where 10 = the highest physical impairment.

**Statistical analyses.** Data analysis was performed using PASW Statistics 18. Descriptive data are shown as the mean ± SD, with the exception of pain and muscle fatigue scores, which are shown as clustered box plots with medians and interquartile ranges. To compare age, height, weight, BMI, Beighton score, PA score, and muscle mass between the groups, independent *t*-tests were used, whereby a significant difference between the EDS-HT and control groups was revealed for PA ($P < 0.001$), which was controlled for in subsequent analyses of muscle function. Consequently, a univariate analysis of covariance was conducted to determine group differences in muscle strength, muscle strength endurance, and functional performance. To compare the number of dropouts for the isokinetic muscle endurance test between both groups, a chi-square test was used. Physical impairment scores were compared by independent *t*-tests. *P* values less than 0.05 were considered statistically significant.

## RESULTS

**Subjects' characteristics.** The anthropometric characteristics of all of the subjects are shown in Table 1. The groups were homogenous with respect to age, sex, height, weight, and BMI. Also, muscle mass of the dominant leg was similar in EDS-HT patients and control subjects ($P = 0.289$). In addition (Table 1), the mean Beighton score was significantly higher ($P < 0.001$) and the PA level was significantly lower ($P < 0.001$) in the patient group compared to the control group, with a range of 1.5–9.7 and 6.1–11.5, respectively.

**Muscle strength.** The results of the muscle strength tests are shown in Table 2. The knee extensor and flexor maximal muscle strength (PT) was significantly lower in the patient group than in the control group at the angular velocity of 60°/second ($P < 0.001$) as well as at 180°/second ($P < 0.001$). The results were even more marked when normalized for body weight (PT/BW), with differences ranging from −33.3% to −42.9%. Reductions were approximately similar for knee extensors and knee flexors. Consequently, the H:Q ratio was not significantly different between both of the groups, although the patient group had lower muscle balance scores than the control group.

**Muscle strength endurance.** Seven EDS-HT patients and none of the control subjects were unable to complete the isokinetic endurance protocol ($P < 0.05$). The results in Table 3 indicated that the EDS-HT patients had significantly reduced isokinetic muscle strength endurance, as expressed by lower total work, and lower work during the first third and last third of the test duration compared

**Table 3. Muscle strength endurance***

| | EDS-HT group | Control group | Difference, % | *P* |
|---|---|---|---|---|
| Isokinetic muscle endurance† | | | | |
| Total work, J | | | | |
| Knee extensors | 1,098 ± 551.0 | 1,636 ± 424.2 | −32.9 | < 0.001‡ |
| Knee flexors | 525 ± 367.2 | 910 ± 301.5 | −42.3 | < 0.001‡ |
| Work first third, J | | | | |
| Knee extensors | 472 ± 260.2 | 680 ± 182.8 | −30.5 | < 0.001‡ |
| Knee flexors | 245 ± 170.6 | 386 ± 141.8 | −36.5 | < 0.001‡ |
| Work last third, J | | | | |
| Knee extensors | 262 ± 132.1 | 406 ± 106.4 | −35.5 | < 0.001‡ |
| Knee flexors | 111 ± 82.3 | 219 ± 68.7 | −49.3 | < 0.001‡ |
| Work fatigue, % | | | | |
| Knee extensors | 34 ± 43.9 | 39 ± 14.8 | | 0.501 |
| Knee flexors | 47 ± 40.3 | 39 ± 23.8 | | 0.276 |
| Static muscle endurance | | | | |
| Dominant hip flexion, seconds | 56 ± 43.6 | 140 ± 60.9 | −60.0 | < 0.001‡ |
| Standing knee flexion, seconds | 35 ± 25.2 | 79 ± 52.9 | −55.7 | < 0.001‡ |

* Values are the mean ± SD unless otherwise indicated. EDS-HT = Ehlers-Danlos syndrome hypermobility type; difference = 100 × ([EDS-HT − control]/control).
† Seven EDS-HT patients were not able to complete the test and were excluded from the analysis.
‡ $P < 0.05$.

to the control subjects, with differences ranging from −30.5% to −49.3%. Conversely, work fatigue, which is the percent decrease in work between the first third and last third of the test, was similar in the EDS-HT and control groups for both knee extensors and knee flexors. Furthermore, static muscle endurance was also markedly reduced in the EDS-HT group as compared to the control group. Actually, the EDS-HT patients could not maintain both postures for even half the time of the control subjects.

**Pain and fatigue.** The results of pain and fatigue associated with the muscle strength and muscle strength endurance tests are shown in Figure 1. Concerning pain severity, the EDS-HT group generally reported mild lower extremity pain at rest just before the test. Immediately after the test, the median pain score increased to 40–60 of 100, which reflects moderate pain due to the test. One minute after the test, pain was only slightly reduced, with 10–20 mm on the VAS. In contrast, the control subjects were pain free at every point in time.

Concerning fatigue, the patient group showed a greater level of fatigue than the control group at every moment. In particular, the EDS-HT group already showed some fatigue at baseline, in contrast to the nonfatigued control group. Immediately after the endurance test, EDS-HT patients were completely exhausted, whereas the control subjects showed only a moderate fatigue. Finally, 1 minute after the test, EDS-HT patients remained exhausted, whereas control subjects quickly recovered. Furthermore, it was striking that the pretest Borg scores in the EDS-HT patient group increased as the protocol moved on.

**Functional performance.** The EDS-HT subjects showed significantly poorer lower body performance than the control subjects, reflected by an increased total time to complete 5 repeated stands from the chair ($P < 0.001$) and an increased average time per stand ($P < 0.001$) (Table 4). The mean ± SD time of 2.3 ± 0.96 seconds in the patient group also suggested a slightly increased risk of falling in these patients.

**Physical impairment.** The mean ± SD overall physical dimension scores were 3.4 ± 1.4 in the EDS-HT group and 0.2 ± 0.2 in the control group ($P < 0.001$). As shown in Figure 2, all subscale physical impairment scores were significantly higher in the EDS-HT group compared to the control group, which indicated poorer physical function in the patient group. The greatest physical impairment was observed in walking and bending and the least physical impairment was observed in self-care activities.

## DISCUSSION

This study demonstrates severely reduced quantitative muscle function and substantial impairment in physical function in patients with EDS-HT compared to age- and sex-matched controls. The patient group clearly shows lower extremity muscle weakness, as evidenced by reduced muscle strength, reduced muscle strength endurance, and diminished functional performance. Lower extremity muscle mass was similar in both groups and therefore unlikely to affect the muscle strength results. In contrast, muscle pain and muscle fatigue were omnipresent in the patient group, increased remarkably due to the muscle strength tests, and decreased very slowly after each test. In addition, poorer physical function was determined in the patient group with the greatest dysfunction in walking and bending, indicating a clinically significant impact on the daily lives of the patients with EDS-HT.

Our results regarding muscle strength are in line with the findings of previous reports on muscle weakness in other types of EDS. Generalized moderate muscle weakness, also including quadriceps muscle weakness, was

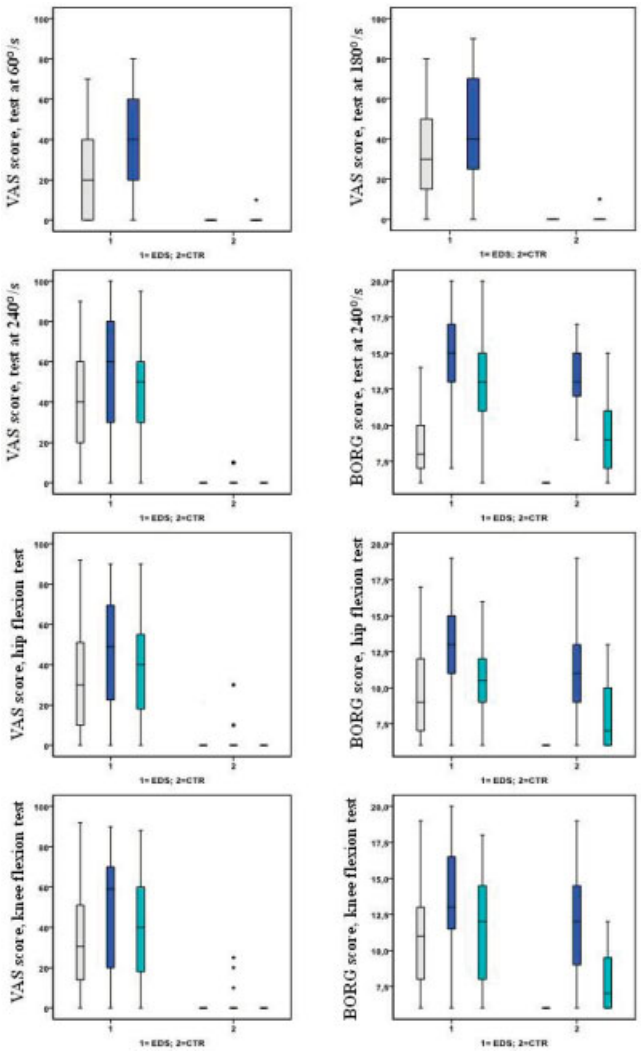


**Figure 1.** Pain and fatigue associated with muscle strength and endurance tests. Clustered box plots are shown with medians and interquartile ranges. Grey bars = just before the test; blue bars = immediately after the test; green bars = 1 minute after the test; VAS = visual analog scale for pain; EDS = Ehlers-Danlos syndrome hypermobility type group; CTR = control group; BORG = Borg scale for fatigue; * = outlier.

shown in 1 case study of the EDS classic type (30) and in 2 patients with the TN-X–deficient EDS type (8). Another study by Voermans et al demonstrated mild to moderate muscle weakness in various EDS types, in which patients with the hypermobility type caused by TN-XB haploinsufficiency were least affected (10). This is peculiar, since by contrast, our results show considerable quadriceps and hamstrings muscle weakness in the EDS-HT group with decreases of 33.3% to 42.9% in maximal muscle strength (PT/BW) compared to the healthy control group. This discrepancy may be explained by the fact that EDS-HT consists of a wide clinical spectrum ranging from very severe to milder phenotypes, in which EDS-HT patients with TN-XB haploinsufficiency represent only a minority. Moreover, the findings of Voermans et al (10) suggest that qualitative variation in muscular involvement among various types of EDS can be a reflection of the tissue-specific distribution of involved molecules, such as TN-X. Unfortunately, the molecular background is still unknown for the majority of patients with EDS-HT (95%).

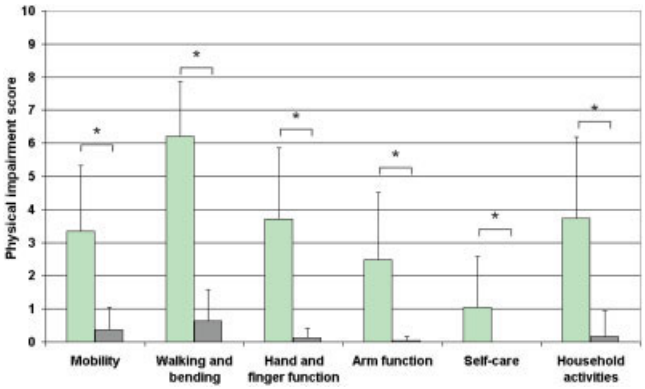


**Figure 2.** Physical impairment. Descriptive statistics are shown as the mean ± SD. Green bars = Ehlers-Danlos syndrome hypermobility type group; grey bars = control group; * = $P < 0.05$.

Furthermore, we did not find a significant difference in the isokinetic H:Q ratio between the patient and control groups. However, compared to the normal H:Q ratio of 60%, muscle imbalance in the EDS-HT group appears to emerge (1-sample *t*-test, $P < 0.05$ at both velocities). Coactivation of the quadriceps and hamstrings is considered to provide active stabilization of the knee when stabilization by the passive restraint system (ligaments and capsule) is lacking (31), which is typical in EDS. However, muscle coactivation can only succeed in stabilizing the knee joint when there is sufficient muscle strength of both the quadriceps and hamstrings. In this case, joint instability in EDS-HT can be explained partially by the substantial muscle weakness in quadriceps and to a larger extent in the hamstrings, as observed in our patients.

Not only maximal strength, but also strength endurance, was remarkably affected in the patients with EDS-HT compared to the healthy subjects. The work capacity in the patients was significantly lower than in the control subjects, at the beginning as well as at the end of the isokinetic endurance test. Surprisingly, the decrease in work, or work fatigue, was similar in the patients and controls. The fact that only data from patients who could complete the test (the "best" patients) were used in the statistical analyses is a plausible explanation for this observation. However, from the static endurance test, it is clear that the patients are easily fatigued, as evidenced by a significantly

**Table 4. Functional muscle performance***

| Chair rise test variable | EDS-HT group | Control group | *P* |
|---|---|---|---|
| Average time per test, seconds | 2.3 ± 0.96 | 1.3 ± 0.24 | < 0.001† |
| Total time, seconds | 8.3 ± 5.21 | 4.2 ± 1.48 | < 0.001† |

* Values are the mean ± SD. EDS-HT = Ehlers-Danlos syndrome hypermobility type.
† $P < 0.05$.

shorter endurance time to maintain a specific posture. Unfortunately, there are currently no studies regarding muscle strength endurance in EDS with which to compare our results.

Several factors may be responsible for the muscle weakness observed in patients with EDS-HT. It has long been suggested that muscle weakness in EDS resulted from reduced PA due to exercise avoidance. In agreement with this hypothesis, the current study showed significantly lower levels of PA in the EDS-HT group. However, after controlling for this level of PA in the statistical analyses, muscle strength remained significantly lower in the patients with EDS-HT. Therefore, it is unlikely that reduced PA would be responsible for the deterioration in muscle function of our EDS-HT patients. In addition, in case of reduced activity, muscle atrophy can occur, and can be responsible for the muscle weakness. However, this is improbable, since DXA measurements of the lower extremity revealed no decreased muscle mass in the EDS-HT patients compared to the controls.

A third and more likely hypothesis could be that the cause of muscle weakness in EDS is located in the ECM of the muscle itself. Abnormalities in muscle ECM composition, based on defective collagen function and a defective interaction with other ECM components, may influence muscle function by altering force transmission (8,10,32). A reduction of the force generated within the muscle fibers and transmitted via tendon onto the skeleton (myotendinous force transmission) can occur due to an increased compliance of the muscle–tendon complex, since more slack has to be taken up before the elastic component can transmit forces. In accordance with this, our research group recently investigated the passive muscle–tendon tissue properties of the plantar flexors in women with EDS-HT. The results show reduced passive muscle tension of the calf muscles, with no difference in muscle cross-sectional area, and a reduced stiffness of the Achilles tendon in patients with EDS-HT compared to healthy control subjects. Structural modifications in the connective tissue of EDS-HT patients are thought to be responsible for this increased muscle–tendon compliance (33). In addition to myotendinous force transmission, up to 40% of the muscle force generated within a muscle can be transmitted from muscle fibers onto the intra-, inter-, and extramuscular connective tissue to the skeleton (myofascial force transmission) (34). Altered compliance of these myofascial pathways might decrease the force transmitted, resulting in muscle weakness. This hypothesis of altered myofascial force transmission is supported by some recent studies in patients with EDS (8,10). Nevertheless, further research is needed.

Other problems may also contribute to the muscle weakness observed in patients with EDS-HT, such as chronic pain and increased fatigability. Our results show that both musculoskeletal pain and fatigue are emphatically present in the EDS-HT group, which is in agreement with previous results in patients with EDS (7,35,36). Pain may cause inhibition of maximal voluntary contraction force, resulting in muscle weakness (37). In addition, a positive and direct relationship between fatigue severity and muscle weakness in EDS has been suggested (38). Moreover, it is striking that the exercise-induced pain and fatigue in the patients with EDS-HT increased disproportionately compared to the muscle performance, and remained extremely high and long-lasting after the effort. The latter points to a delayed recuperation in EDS-HT. The reason for pain and fatigue remains unclear, but it could be that mitochondrial dysfunction is involved, as suggested in fibromyalgia. Mitochondrial dysfunction can account for a lower production rate of ATP in the muscle and nervous systems, which is associated with increased peripheral fatigue and pain (39). In any case, this warrants further investigation.

This study was not only focused on weakness in muscle strength and muscle strength endurance, but also on the impact of these factors on the patients' functional capacities in daily life. Knee extensor muscle weakness has been associated with a reduction in walking capacity, stair climbing ability, getting up from a seated position, postural stability, and even the occurrence of falls (14–17). In agreement, our results show a significantly poorer functional performance on the chair rise test in the patients with EDS-HT compared to the control subjects, as evidenced by the increased total and average time to stand up from and sit down on a chair. Indirectly, a slightly increased risk of falling was determined, which can be confirmed by a recent study that demonstrated increased falls and imbalance in patients with EDS-HT (40). In addition, the AIMS scores demonstrated impaired physical function in the EDS-HT patients, with the highest impairment in walking and bending, which are activities in which quadriceps and hamstrings muscle strength plays an important role. This explains why supportive aids, such as crutches or a wheelchair, regularly appeal to many patients with EDS (41).

The fact that reduced muscle strength is a major contributor to physical impairment in EDS-HT, which significantly affects the daily lives of EDS-HT patients, may be a starting point for appropriate treatment. EDS-HT has no definitive treatment and therefore poses a management challenge. In light of our findings, it may be appropriate for clinicians to consider interventions that improve muscle strength and muscle strength endurance, and at the same time diminish pain and fatigue, which are known to compromise improvement of muscle strength. Several studies have shown that in patients with rheumatoid arthritis and fibromyalgia, both aerobic training and resistance training, on land as well as in water, improve muscle strength, endurance capacity, functionality, and health-related quality of life (42–46). However, in adult patients with a heritable connective tissue disorder, whether muscle function can be improved by training and to what extent, and thereby improve physical function, requires evaluation in future studies.

Our results must be viewed within the limitations of the study. First, the current data are limited to the lower extremity, whereas muscle strength in the upper extremity may or may not be affected in patients with EDS-HT. Second, our cross-sectional results may be affected by reverse causation, i.e., physical function limitations could adversely affect muscle strength. Third, the present study only included female patients, so we should be cautious

with generalization of the results. However, 90% of patients with EDS-HT are women (4).

In conclusion, this is the first extensive clinical study on lower extremity quantitative muscle function in patients with EDS-HT. The results demonstrate considerably reduced quadriceps and hamstrings muscle strength and muscle strength endurance in the EDS-HT patients compared to the healthy subjects, which was also reflected in poorer functional performance and impaired physical function. The muscle weakness may be due to muscle dysfunction rather than muscle atrophy, in which altered force transmission due to abnormalities in muscle extracellular matrix composition may play an important role. Further research is needed to investigate whether exercise programs to strengthen quadriceps and hamstrings can improve muscle function in patients with EDS-HT.

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### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms Rombaut had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## REFERENCES

1. Beighton P, De Paepe A, Hall JG, Hollister DW, Pope FM, Pyeritz RE, et al. Molecular nosology of heritable disorders of connective tissue. Am J Med Genet 1992;42:431–48.
2. Steinmann B, Royce PM, Superti-Furga A. The Ehlers-Danlos syndrome. In: Royce P, Steinmann B, editors. Connective tissue and its heritable disorders: molecular, genetic and medical aspects. New York: Wiley-Liss; 1993. p. 351–407.
3. Grahame R. Heritable disorders of connective tissue. Baillieres Best Pract Res Clin Rheumatol 2000;14:345–61.
4. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ, for the Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Ehlers-Danlos syndrome: revised nosology, Villefranche, 1997. Am J Med Genet 1998; 77:31–7.
5. Callewaert B, Malfait F, Loeys B, De Paepe A. Ehlers-Danlos syndromes and Marfan syndrome. Best Pract Res Clin Rheumatol 2008;22:165–89.
6. Rombaut L, Malfait F, Cools A, De Paepe A, Calders P. Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 2010;32:1339–45.
7. Rombaut L, Malfait F, De Paepe A, Rimbaut S, Verbruggen G, De Wandele I, et al. Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: a comparative study with fibromyalgia and rheumatoid arthritis. Arthritis Rheum 2011;63:1979–87.
8. Voermans NC, Altenburg TM, Hamel BC, de Haan A, van Engelen BG. Reduced quantitative muscle function in tenascin-X deficient Ehlers-Danlos patients. Neuromuscul Disord 2007;17:597–602.
9. Voermans NC, Bonnemann CG, Huijing PA, Hamel BC, van Kuppevelt TH, de Haan A, et al. Clinical and molecular overlap between myopathies and inherited connective tissue diseases. Neuromuscul Disord 2008;18:843–56.
10. Voermans NC, van Alfen N, Pillen S, Lammens M, Schalkwijk J, Zwarts MJ, et al. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Ann Neurol 2009;65:687–97.
11. Zweers MC, Bristow J, Steijlen PM, Dean WB, Hamel BC, Otero M, et al. Haploinsufficiency of TNXB is associated with hypermobility type of Ehlers-Danlos syndrome. Am J Hum Genet 2003;73:214–7.
12. Berglund B, Nordstrom G, Lutzen K. Living a restricted life with Ehlers-Danlos syndrome (EDS). Int J Nurs Stud 2000;37: 111–8.
13. Rombaut L, Malfait F, De Wandele I, Cools A, Thijs Y, De Paepe A, et al. Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. Arch Phys Med Rehabil 2011;92:1106–12.
14. Madsen OR, Egsmose C. Associations of isokinetic knee extensor and flexor strength with steroid use and walking ability in women with rheumatoid arthritis. Clin Rheumatol 2001; 20:207–12.
15. Jones CJ, Rutledge DN, Aquino J. Predictors of physical performance and functional ability in people 50+ with and without fibromyalgia. J Aging Phys Act 2010;18:353–68.
16. Brown M, Sinacore DR, Host HH. The relationship of strength to function in the older adult. J Gerontol A Biol Sci Med Sci 1995;50:55–9.
17. Wolfson L, Judge J, Whipple R, King M. Strength is a major factor in balance, gait, and the occurrence of falls. J Gerontol A Biol Sci Med Sci 1995;50:64–7.
18. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36:936–42.
19. Wilhite MR, Cohen ER, Wilhite SC. Reliability of concentric and eccentric measurements of quadriceps performance using the Kin-Com dynamometer: the effect of testing order for three different speeds. J Orthop Sports Phys Ther 1992;15:175–82.
20. Biodex Medical Systems. Isokinetic testing and data interpretation: data analysis. URL: http://www.biodex.com/sites/default/files/data.pdf.
21. Nosse L. Assessment of selected reports on the strength relationship of the knee musculature. J Orthop Sports Phys Ther 1982;4:78–85.
22. Maquet D, Forthomme B, Demoulin C, Jidovtseff B, Crielaard JM, Croisier JL. Isokinetic strength and fatigue of the elbow flexors and extensors in sedentary women. Isokinet Exerc Sci 2004;12:203–8.
23. Maquet D, Croisier JL, Renard C, Crielaard JM. Muscle performance in patients with fibromyalgia. Joint Bone Spine 2002; 69:293–9.
24. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4:407–14.
25. Borg G. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.
26. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy x-ray absorptiometry method. Am J Clin Nutr 2002;76: 378–83.
27. Novotec Medical. Chair rising test (CRT): Leonardo Mechanography ground reaction force platform (GRFP) v4.1.19. 2006.
28. Riemsma RP, Taal E, Rasker JJ, Houtman PM, Van Paassen HC, Wiegman O. Evaluation of a Dutch version of the AIMS2 for patients with rheumatoid arthritis. Br J Rheumatol 1996; 35:755–60.
29. Pouchot J, Guillemin F, Coste J, Bregeon C, Sany J, for the "Quality of Life in Rheumatology" Task Force. Validation of the French version of the Arthritis Impact Measurement Scales 2 and comparison with the French version of the

Nottingham Health Profile. Rev Rhum Engl Ed 1996;63:389–404.
30. Bilkey WJ, Baxter TL, Kottke FJ, Mundale MO. Muscle formation in Ehlers-Danlos syndrome. Arch Phys Med Rehabil 1981;62:444–8.
31. Riemann BL, Lephart SM. The sensorimotor system, part I: the physiologic basis of functional joint stability. J Athl Train 2002;37:71–9.
32. Huijing P, Voermans N, Baan G, Buse T, van Engelen B, de Haan A. Muscle characteristics and altered myofascial force transmission in tenascin-X-deficient mice, a mouse model of Ehlers-Danlos syndrome. J Appl Physiol 2010;109:986–95.
33. Rombaut L, Malfait F, De Wandele I, Mahieu N, Thijs Y, Segers P, et al. Muscle–tendon tissue properties in the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken) 2012;64:766–72.
34. Purslow PP. Muscle fascia and force transmission. J Bodyw Mov Ther 2010;14:411–7.
35. Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. Semin Arthritis Rheum 2010;40:267–74.
36. 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; 40:370–8.
37. Graven-Nielsen T, Lund H, Arendt-Nielsen L, Danneskiold-Samsoe B, Bliddal H. Inhibition of maximal voluntary contraction force by experimental muscle pain: a centrally mediated mechanism. Muscle Nerve 2002;26:708–12.
38. Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: an explorative study. Physiotherapy 2011;97: 170–4.
39. Cordero MD, de Miguel M, Carmona-Lopez I, Bonal P, Campa F, Moreno-Fernandez AM. Oxidative stress and mitochondrial dysfunction in fibromyalgia. Neuro Endocrinol Lett 2010;31:169–73.
40. Rombaut L, Malfait F, De Wandele I, Thijs Y, Palmans T, De Paepe A, et al. Balance, gait, falls, and fear of falling in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken) 2011;63:1432–9.
41. Ainsworth SR, Aulicino PL. A survey of patients with Ehlers-Danlos syndrome. Clin Orthop Relat Res 1993;286:250–6.
42. Rooks DS, Silverman CB, Kantrowitz FG. The effects of progressive strength training and aerobic exercise on muscle strength and cardiovascular fitness in women with fibromyalgia: a pilot study. Arthritis Rheum 2002;47:22–8.
43. Kingsley JD, Panton LB, Toole T, Sirithienthad P, Mathis R, McMillan V. The effects of a 12-week strength-training program on strength and functionality in women with fibromyalgia. Arch Phys Med Rehabil 2005;86:1713–21.
44. Gusi N, Tomas-Carus P, Hakkinen A, Hakkinen K, Ortega-Alonso A. Exercise in waist-high warm water decreases pain and improves health-related quality of life and strength in the lower extremities in women with fibromyalgia. Arthritis Rheum 2006;55:66–73.
45. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum 2009;61:1726–34.
46. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol 2011;30: 623–32.