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Does muscle strength change over time in patients with hypermobile Ehlers-Danlos syndrome/ Hypermobility Spectrum Disorder? An 8-year follow-up study.

Running head: Evolution of muscle strength in hEDS/HSD

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ABSTRACT

Objective: Reduced maximal muscle strength and strength endurance has been found in patients with hypermobile Ehlers-Danlos syndrome/Hypermobility Spectrum Disorder (hEDS/HSD) and is recognized as a common associated feature of the disorder. However, it is currently not documented to which extent these parameters change over time. Therefore, an 8-year follow-up study was performed to investigate this evolution.

Methods: Thirty female patients (mean age: 41 years) with hEDS/HSD and 17 controls participated at baseline and eight years later. Maximal muscle strength and strength endurance tests of the knee flexors and extensors (Biodex), and two lower limb posture maintenance tests were performed to evaluate static strength endurance. In addition, muscle mass and density were evaluated by dual-energy X-ray absorptiometry and peripheral quantitative computed tomography.

Results: Maximal muscle strength and strength endurance were significantly lower at both baseline and follow-up in the hEDS/HSD group compared to the control group ($p \leq 0.007$). Maximal muscle strength of the knee flexors (decreased in the control group: η^2 : 0.139), strength endurance of the knee extensors (decreased in the hEDS/HSD group and increased in the control group: η^2 : 0.244) and muscle density (decreased in the hEDS/HSD group: η^2 : 0.263) showed a significantly different evolution over eight years. No other significant differences in evolution were found.

Conclusion: Decreased muscle strength was identified at both time points in patients with hEDS/HSD. The evolution of most muscle strength parameters over time did not significantly differ between groups. Future studies should focus on effectiveness of different types of muscle training strategies in hEDS/HSD patients.

SIGNIFICANCE AND INNOVATIONS

- Patients with hEDS/HSD demonstrate substantially higher pain scores, greater functional impairment and reduced lower extremity muscle strength continuing over an 8 year period in comparison with CTR
- Patients with hEDS/HSD show no muscle atrophy or higher muscle lipid content in comparison with CTR
- Muscle strength parameters remain relatively stable in patients with hEDS/HSD after an 8 year period, in which several factors may play a role such as physiotherapy and exercises.

Ehlers-Danlos syndrome is a heterogeneous group of hereditary connective tissue disorders caused by mutations in the genes encoding for collagen or enzymes involved in the processing or modification of

collagen. Hence, the most important consequences are joint hypermobility, tissue fragility and skin hyperextensibility (1). The current EDS classification distinguishes 13 subtypes, caused by defects in 19 different genes (2). However, the genetic basis of the hypermobile type of EDS, which is the most common subtype, remains largely unknown and is therefore based on clinical criteria.

Over time, these clinical criteria have been revised in order to describe hypermobile EDS in detail and to delineate it from related conditions. Initially, 'the hypermobility type of Ehlers-Danlos syndrome' (EDS-HT) was described based on its major and minor clinical characteristics, which include generalized joint hypermobility and a hyperextensible or soft velvety skin (major criteria), a positive family history, recurrent joint dislocations, and chronic pain (minor criteria) (1). In 2017, the description was refined and now also emphasises associated soft tissue fragility (e.g. multiple abdominal hernias, prolapse of organs at the level of the pelvic floor, etc.) (2). By consensus, the hypermobile type of EDS is now referred to as 'hypermobile EDS' (hEDS). Patients with a previous diagnosis of EDS-HT who no longer fully meet the stricter 2017 criteria for hEDS, are now described as having 'Hypermobility Spectrum Disorder' (HSD). Consequently, a group of patients diagnosed with EDS-HT in the past now consist of patients with hEDS and HSD.

In addition to generalized joint hypermobility and recurrent joint dislocations, patients with hEDS/HSD report multiple other musculoskeletal symptoms and problems. In 2012, Rombaut et al. identified reduced maximal muscle strength and muscle strength endurance in 43 patients with hEDS/HSD, compared to healthy controls (3). This decrease may result from musculoskeletal pain and exercise avoidance and is likely to be related to abnormalities of the extracellular matrix (ECM) of the muscle (2, 4, 5). By illustration, a study by Rombaut and colleagues found an increased tendon extensibility in patients with hEDS/HSD compared to controls, which may lead to a decreased efficiency in force transmission (6). Another argument that supports the link between decreased muscle strength and connective tissue involvement, is that mild-to-moderate neuromuscular involvement has also been found in several other types of EDS (4).

Unfortunately, decreased muscle strength further compromises joint stability and contributes to altered movement patterns and overload injuries in this patient population. Moreover, reduced maximal muscle strength and muscle strength endurance, muscle cramps, ruptures and pain are related to activity limitations in hEDS/HSD (3, 5). Although Castori et al. (2010; 2013) mentioned muscle weakness as part of the disease progression in hEDS/HSD, longitudinal studies about the evolution of muscle weakness over time are lacking (7-9). As muscle weakness is a major contributor to functional impairment, knowledge of how muscle strength changes over time may provide a crucial understanding of the quality of life, prognosis and follow-up of patients with hEDS/HSD (3). Therefore, this longitudinal study aimed to

investigate the evolution of maximal muscle strength, muscle strength endurance, muscle mass and density in patients with hEDS/HSD over a period of eight years.

PATIENTS AND METHODS

1. Participants

This study protocol was reviewed and approved by the Ethical Committee of Ghent University Hospital (EC number 2017/1278), and written informed consent was obtained from all participants. Female patients diagnosed according to the Villefranche criteria, and controls matched for sex and age were selected in 2009-2010 (at baseline or T1), as described by Rombaut et al. (2012) (3). In 2017 (at follow-up or T2), patients and healthy controls (CTR) were contacted a second time. Thirty patients with hEDS/HSD and 17 CTR participated again at T2 (follow-up rate of 70% or n=30/43 and 40% or n=17/43 respectively). The main reasons for drop out were: no up-to-date contact details, work commitments or no interest. Of the 30 patients previously diagnosed with EDS-HT, ten patients had a hEDS diagnosis according to the 2017 EDS nosology, while 20 were reclassified as having HSD (2,9). No differences in muscle characteristics between participants with hEDS and HSD were found. Due to the small group hEDS patients (n=10), further analyses were performed on the total patient group, referred to as 'hEDS/HSD' in this paper.

2. Procedure

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Participants were invited by e-mail or phone to participate in this follow-up study at Ghent University Hospital. A few weeks before the measurements, each participant was asked to fill in a self-developed follow-up questionnaire evaluating physiotherapy, sports, physical activities and medical history (injuries, surgeries and pregnancies) over the past eight years.

Subject characteristics, including age, height, weight and body mass index (BMI) were collected. Lean mass dominant leg (LMDL; kg) and subtotal lean mass (whole body without the head (SLM); kg) were evaluated by total body dual x-ray absorptiometry (DXA) with a Hologic QDR-Discovery device (software version 2.3.1; Hologic, Bedford, MA, USA) (3). Furthermore, muscle density of the dominant leg (mg/cm^3), which reflects the lipid content of the muscle (the lower the muscle density, the higher the lipid content), was measured by peripheral quantitative computed tomography (pQCT) with a XCT-2000 device (Stratec, Medizintechnik, Pforzheim, Germany) (10). Subsequently, participants were evaluated according to the protocol described below.

3. Measurements

Prior to the measurements, general average *pain* severity on the day of the tests was measured using a visual analog scale (VAS, mm) (3).

Maximal muscle strength of the knee flexors (Hamstrings; FL) and extensors (Quadriceps; EX) was evaluated by isokinetic tests (Biodex) at an angular velocity of $60^\circ/\text{sec}$ and five repetitions following the protocol described by Rombaut et al. (2012). If test results showed a coefficient of variation higher than 15%, the test was repeated (11). Absolute peak torque (PT; Nm), i.e. the highest force output accomplished by the muscle at any moment during a repetition, was assessed and PT/SLM (Nm/kg) and PT/LMDL (Nm/kg) were calculated for both knee flexion and extension.

Muscle strength endurance of the FL and EX was evaluated by isokinetic tests at an angular velocity of $240^\circ/\text{sec}$ and 30 repetitions, and of the lower limb muscles by two posture maintenance tests in which participants had to hold a posture as long as possible, as explained by Rombaut et al. (2012). For the isokinetic tests, the amount of work performed during all 30 repetitions (total work; J), the first ten repetitions (work first third; J) and last ten repetitions (work last third; J) and the ratio of difference between those first and last ten repetitions or work fatigue (%) were assessed for the knee flexors and extensors. For the posture maintenance tests, the length of time (sec) during which a patient could maintain the correct position was recorded. Relative values (normalized for SLM and LMDL) were calculated for total work (J/kg) and work fatigue (%/kg), and for SLM for posture maintenance (sec/kg).

Additionally, pain severity (VAS) was evaluated before and immediately after each muscle strength test and 1 minute after each muscle endurance test. Finally, *physical activity* and *functional impairment* were respectively evaluated by the Baecke questionnaire and Arthritis Impact Measurement Scales (AIMS) (3). The mobility, walking and bending, hand, finger and arm function subscales of the AIMS as well as the total Baecke score were used for analyses.

4. Statistical analyses

Data analysis was performed using the statistical package SPSS version 24. Normality was evaluated using the Shapiro-Wilk test and Q-Q plots. Data (normally distributed) are shown as mean \pm SD, except for the AIMS questionnaire (not normally distributed), which is shown as medians and interquartile ranges. Pain scores are shown as clustered box plots with medians and interquartile ranges. As all statistical assumptions were fulfilled, repeated measures ANOVA was performed to identify significant differences in evolution between both groups (hEDS/HSD and CTR). From a clinical point of view age, pain and BMI are important factors impacting muscle strength. However, due to a small sample size, only the variable with the biggest impact (BMI) was included as a covariate. Post hoc paired-sample T tests with Bonferroni correction were executed when a significant interaction (time*group) effect was observed, in order to identify significant time effects within either the hEDS/HSD group or CTR group. For the AIMS questionnaire, a non-parametric Wilcoxon test was performed to identify significant time effects and Mann-Whitney's U test for group differences on T1 and T2 and for the difference scores of the two time points between hEDS/HSD and the CTR group, all with Bonferroni correction. P values less than 0.05 were considered statistically significant. Additionally, size effect estimates are shown by partial eta squared (η^2) for repeated measures ANOVA and eta squared (η^2) for Mann-Whitney's U test, of which values of 0.01, 0.06 and 0.14 represent small, medium and large size effects respectively (12). Finally, results of the follow-up questionnaires were analyzed by descriptive statistics (frequency tables) and pain severity scores before and after the muscle strength tests by an independent samples T test.

RESULTS

1. Characteristics

Subject characteristics at both T1 and T2 are presented in Table 1. There were no significant differences between the patient and CTR group at baseline nor at follow-up, except for a significantly higher Beighton score in the patient group in comparison with the CTR group at T1 ($p < 0.001$). The evolution in muscle density was significantly different between the hEDS/HSD and CTR group (p time*group=0.001, η^2 : 0.263),

with a mild decrease in muscle density in the hEDS/HSD group over time ($p < 0.001$), but not in the CTR group. Over eight years, SLM increased significantly (main effect for time: $p = 0.012$), with a similar evolution for both groups.

2. Maximal muscle strength

Maximal muscle strength results are presented in Table 2. The repeated measures analysis of variance showed a significant group effect for all maximal muscle strength variables, indicating that the hEDS/HSD group was significantly weaker than the CTR at baseline and follow-up (main effect for group: $p \leq 0.011$).

The evolution of most maximal muscle strength variables did not significantly differ between patients and CTR, except for the peak torque of the FL and these normalized for LMDL ($p_{\text{time*group}} = 0.012$, $\eta^2 = 0.139$ and $p_{\text{time*group}} = 0.045$, $\eta^2 = 0.099$ respectively) due to a significant decline over eight years in the CTR group ($p = 0.052$ and $p = 0.028$ respectively) whereas the patient group appeared to remain stable ($p = 1.000$). Furthermore, no changes over time were observed.

3. Muscle strength endurance (supplementary table)

Muscle strength endurance results are presented in the supplementary table. Absolute and relative values of total work and work performed in the first and last ten repetitions were significantly lower in the hEDS/HSD group compared to the CTR at baseline and follow-up (main effect for group: $p \leq 0.004$). Work fatigue, expressed as a ratio of difference between the work first third and last third (absolute and relative values), did not significantly differ between the two groups at T1 and T2, except for work fatigue of the FL normalized for SLM and LMDL ($p = 0.045$ and $p = 0.028$ respectively).

A significant different evolution of total work (absolute and relative values) and work in the first and last third performed by the EX was identified ($p_{\text{time*group}} \leq 0.022$, η^2 varying between 0.121 - 0.363; figure 1). Post hoc tests showed a decrease of total work and work first third performed by the EX in the patient group ($p = 0.006$ and $p = 0.002$ respectively), in contrast to an increase of total work and work last third in the CTR group over eight years ($p = 0.010$ and $p = 0.032$ respectively). No differences in evolution for the FL were observed. Work fatigue (absolute and relative values) of the extensors and flexors showed a similar evolution and no significant changes over time except for work fatigue of the FL which significantly improved over time (main effect for time: $p = 0.025$).

Posture maintenance tests (absolute and relative values) showed significantly lower values in the hEDS/HSD group compared to the CTR group over both time points (main effect for group: $p < 0.001$). No significant differences in evolution or over time were found between both groups.

4. Pain associated with maximal muscle strength and muscle strength endurance tests.

Pain severity was significantly higher at baseline and follow-up in the patient group in comparison with the CTR group, both before and after the strength tests ($p < 0.001$, figure 2).

5. Questionnaires

Results of the questionnaires are presented in Table 3. Functional impairment ($p < 0.001$) and pain were significantly higher and physical activity significantly lower in the hEDS/HSD group compared to the CTR group at baseline and follow-up (main effect for group: $p \leq 0.001$). All variables showed no significant different evolution between the two groups and no significant changes over time.

Results on the follow-up questionnaire showed that over eight years, 40% of the patients reported they received physiotherapy multiple times a week, 20% weekly, 13.3% monthly and 16.7% incidentally. This is in contrast to the CTR, of which 0% received physiotherapy weekly or monthly and 64.7% incidentally. Physiotherapy sessions were reported to consist mainly of stabilisation exercises (hEDS/HSD: 60%, CTR: 23.5%), manual therapy (hEDS/HSD: 56.7%, CTR: 58.8%), muscle strength training (hEDS/HSD: 53.3%, CTR: 17.6%) and massage (hEDS/HSD: 50%, CTR: 0%). Additionally, 33.3% of the patients performed exercises multiple times a week, 20% weekly and 10% monthly, whereas 5.9% of the CTR exercised multiple times a week or weekly and 0% monthly. The most commonly reported sports and physical activities undertaken by the participants included walking (hEDS/HSD: 60%, CTR: 70.6%), cycling (hEDS/HSD: 46.6%, CTR: 76.5%), swimming (hEDS/HSD: 43.3%, CTR: 41.2%) and aquagym/hydrotherapy (hEDS/HSD: 26.7%, CTR: 0%). Regarding their medical history over the eight years, compared to the CTR group, more of the patient group reported experiencing injuries (hEDS/HSD: 56.7%, CTR: 47.1%) and one or more (any type of) surgeries (hEDS/HSD: 56.1%, CTR: 35.3%). Similar proportions of each group also reported having given birth to one or more children over the eight years (hEDS/HSD: 13.4%, CTR: 11.8%).

DISCUSSION

This study has provided new insight into the evolution of muscle strength over a period of eight years in patients with hEDS/HSD in comparison with CTR. In general, at baseline and follow-up, maximal muscle

strength and muscle strength endurance were significantly lower in patients than in CTR. The main finding of this study is that the strength parameters remained relatively stable in the patient group over a period of eight years.

Maximal muscle strength and muscle strength endurance in patients compared to healthy controls

Similar to the baseline results, maximal muscle strength and muscle strength endurance generally remained significantly lower at follow-up in the hEDS/HSD group in comparison with the CTR group. Several factors may be responsible for reduced muscle strength in hEDS/HSD (3).

As suggested by Rombaut et al. (2012), musculoskeletal pain related to joint hypermobility, subluxations and central sensitization processes may contribute to lower muscle strength by inhibiting maximal voluntary contraction force (3, 4, 13, 14). This is in accordance with our results, showing significantly higher VAS scores before and after the muscle strength tests in comparison with the CTR group. Future research focusing on strength generation in (asymptomatic) hypermobile individuals could further explore this impact.

Furthermore, this study identified lower habitual physical activity levels in the hEDS/HSD group in comparison with the CTR, which may lead to deconditioning and decreased muscle strength (15).

When results on DXA scans were compared the CTR, this study did not identify any signs of muscle atrophy in the hEDS/HSD group, which is in accordance with previous studies (1, 3, 4, 16-18). Therefore, it is less likely that muscle atrophy could provide an explanation for the observed lower muscle strength in hEDS/HSD.

In addition, alterations in the structural integrity of the connective tissue in the tendons and surrounding the muscle cells could contribute to a reduced force transmission from the muscle fibers onto the skeleton, eventually leading to an altered muscle function and reduced muscle strength (3, 4, 19, 20). Poor proprioception, associated with generalized joint hypermobility, may be related to reduced muscle strength as well (19).

Evolution of maximal muscle strength

The present study did not demonstrate any significant changes in maximal muscle strength over time in hEDS/HSD patients. However, a decrease of maximal muscle strength generated by the knee flexors was identified in the CTR group.

Though a decrease of maximal strength in the CTR could be explained by an age-related deterioration of muscle function, this decline appears to be absent in the hEDS/HSD group (21-23). The high engagement with physiotherapy and exercise in the hEDS/HSD group could give a likely explanation, as these are major contributors to the maintenance of muscle strength and mass over time and which are prescribed as an important aspect in the multidisciplinary treatment of the pathology (24, 25). Furthermore, more than half of the physiotherapy consultations consisted of muscle strengthening exercises in the patient group, in contrast to 18% in the CTR group. Although no information is available about exact methods of this strength training and accomplished strength enhancements, these findings only suggest that physiotherapy and exercise could have a positive impact in preventing further deterioration of maximal muscle strength in hEDS/HSD.

Evolution of muscle strength endurance

In general, this study identified no differences over time in static muscle strength endurance and muscle strength endurance of the knee flexors in both groups. However, decreased muscle strength endurance of the knee extensors in the hEDS/HSD group was observed, which is in contrast to the increase in the CTR group over a period of eight years.

The evolution of muscle strength endurance over time in the CTR group could be contributed to age-related changes in muscle fiber type. Findings about changes of type I muscle fibers, mainly used during daily living and aerobic endurance activities, are inconclusive but range from a higher type I/type II fiber ratio to non-affected type I fibers during the aging process (25-27). This eventually could result in an increase or stabilization of muscle strength endurance, as shown in the CTR group of this study.

By contrast, in the patient group, muscle strength endurance of the knee extensors significantly decreased over the period of eight years (total work and work in the first third of the isokinetic test). This might be explained by the content of the physiotherapy sessions in hEDS/HSD patients participating in this study as this mainly focused on joint stability exercises (60%) and manual therapy (56.7%) over the past eight years rather than improving muscle strength endurance, which is in accordance with research identifying smaller distances performed in the six minute walking test in comparison with healthy CTR (19). Furthermore, the implementation of cognitive-behavioral treatment (CBT) including coping strategies in the multidisciplinary treatment program for hEDS/HSD could provide a likely explanation why results on the strength endurance tests were lower (28-30). It could be hypothesized that the decrease of total work over a period of eight years in the hEDS/HSD group can be attributed to coping strategies learned in physiotherapy sessions to

avoid maximal load on the muscles and unstable joints. Decreased work in the first third might reflect that patients with hEDS/HSD possibly try to spread the load over time in order to be able to perform the entire test consisting of 30 repetitions. However, CBT was not evaluated in this study, therefore this hypothesis remains purely speculative.

Clinical implications

In addition to the fact that pain and fatigue frequently occur in hEDS/HSD, reduced muscle strength is a major contributor to functional impairment and has a considerable impact on the daily living activities of these patients (3, 14, 19, 31). For instance, as Hamstring muscles play a major role in power transfer in the lower extremity, muscle weakness could lead to altered motor control and propulsion in these patients (19, 32). Therefore, treatment focusing on pain relief, joint stabilization exercises, coping strategies and muscle strengthening exercises could be recommended in order to improve quality of life and reduce disability (9, 19, 33). Physiotherapy plays a key role within the multidisciplinary team in the management of this patient population (33). A pilot study performed by Bathen et al. (2013) showed positive effects on daily functioning, kinesiophobia and both muscle strength and endurance after an intensive training program with learning coping strategies. They suggest that improving muscle function in hEDS/HSD is possible (29). Furthermore, endurance training in order to improve cardiovascular, physical and musculoskeletal fitness should be included in the training program as we observed a longitudinally decreased muscle strength endurance in hEDS/HSD (33). However, evidence-based clinical trials evaluating intervention programs are scarce. Therefore, further research should determine whether or not exercise is effective in this patient group and which types of exercises should be recommended, specifically to improve maximal muscle strength and muscle strength endurance in hEDS/HSD.

Strengths and limitations

This was the first longitudinal study evaluating muscle strength parameters in patients with hEDS/HSD over eight years, with a high follow-up rate of the patients with hEDS/HSD. Along with objective measurements of muscle strength, this study also retrospectively questioned several muscle strength related parameters. However, the results of the study should be viewed within the limitations of the study. First, the use of this self-developed follow-up questionnaire could create a bias due to the dependence on the patient's ability to recall this information. Secondly, patients were only measured twice over a period of eight years. Future studies should systematically evaluate medical parameters, muscle strength and muscle mass preferably each year in order to better evaluate the evolution in this patient population. Thirdly, a low follow-up rate of CTR was achieved. However, no significant differences in outcomes (measured at T1) were observed

between the drop outs and the follow-up participants, either in the patient group and the control group. Though the power of this study is decreased by this drop out, especially in the control group, the impact of this low follow-up rate is therefore probably limited. Finally, results cannot be generalized to the upper limb, as only the lower limb was evaluated.

Conclusion

In conclusion, this follow-up study showed at baseline and follow-up a significant reduced muscle strength and muscle strength endurance in hEDS/HSD patients compared to the CTR, of which the underlying causes are possibly multifactorial. With regard to the evolution, the majority of the strength parameters remained relatively stable in the patient group over a period of eight years. Future studies should focus on both effectiveness and efficiency of different types of muscle training strategies and their effect on pain and functioning in hEDS/HSD patients.

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TABLES

Table 1: Subject characteristics

	<i>hEDS/HSD group</i>		<i>CTR group</i>		P time	P group	P time*group
	T1	T2	T1	T2			
Age, years	41.3 ± 11.39	49.2 ± 11.36	40.65 ± 11.66	48.65 ± 11.78	<0.001*	0.892	0.398
BMI, kg/m ²	27.3 ± 6.14	28.7 ± 5.79	24.5 ± 3.99	25.9 ± 4.93	0.011*	0.087	0.981
Beighton (/9)	6.7 ± 1.65°	4.2 ± 2.17	1.4 ± 1.62	NA	NA	NA	NA
SLM, kg	40.9 ± 6.31	43.2 ± 7.71	43.1 ± 5.71	44.8 ± 6.12	0.012*	0.340	0.679
LMDL, kg	7.3 ± 1.33	7.5 ± 1.46	7.9 ± 1.22	8.0 ± 1.15	0.131	0.211	0.446
Muscle density, mg/cm ³	76.6 ± 2.34	74.3 ± 3.25	76.6 ± 1.65	76.7 ± 1.83	0.002*	0.101	0.001*

Data are shown as mean ± SD. hEDS/HSD: patient group; CTR: control group; BMI = Body Mass Index; SLM = Subtotal Lean Mass; LMDL = Lean Mass Dominant Leg; T1 = at baseline (2009); T2 = at follow-up (2017); Kg: kilogram; NA: not applicable (measurements were not performed at T2); P time: P value for comparison T2 with T1; P group: hEDS/HSD compared with CTR group; P time*group = P value of comparison evolution between hEDS/HSD and CTR group, *: P <0.05; °: P value <0.05 of hEDS/HSD compared with CTR group at T1 (analysed by an independent samples T test)

Table 2: Maximal muscle strength – absolute and relative values

PT	hEDS/HSD group		CTR group		P time	P group	P time*group	p η^2
	T1	T2	T1	T2				
Isokinetic test at an angular velocity of 60°/sec								
EX, Nm	85.3 ± 36.97	84.7 ± 31.12	128 ± 23.09	119.3 ± 23.39	0.986	<0.001*	0.271	0.028
FL, Nm	44.2 ± 21.43	45.4 ± 15.35	65.7 ± 14.18	58.7 ± 15.97	0.068	<0.001*	0.012*	0.139
EX/SLM, Nm/kg	2.1 ± 0.83	1.9 ± 0.62	2.9 ± 0.52	2.7 ± 0.52	0.613	0.001*	0.681	0.004
FL/SLM, Nm/kg	1.1 ± 0.45	1.1 ± 0.28	1.5 ± 0.26	1.3 ± 0.33	0.750	0.007*	0.066	0.084
EX/LMDL, Nm/kg	11.7 ± 4.39	11.1 ± 3.54	16.0 ± 2.69	14.9 ± 2.73	0.556	0.001*	0.761	0.002
FL/LMDL, Nm/kg	6.0 ± 2.25	6.1 ± 1.67	8.2 ± 1.39	7.1 ± 1.80	0.707	0.011*	0.045*	0.099

Data are shown as mean ± SD. hEDS/HSD: patient group; CTR: control group; PT: Peak torque; SLM = Subtotal Lean Mass; LMDL = Lean Mass Dominant Leg; EX: knee extensors; FL: knee flexors; T1 = at baseline (2009); T2 = at follow-up (2017); Nm: Newton meter; Kg: kilogram; P time: P value of comparison T2 with T1, P group: hEDS/HSD compared with CTR group, P time*group: P value of comparison evolution between hEDS/HSD and CTR group with BMI as covariate, *: P <0.05; p η^2 : partial eta squared (relative size effect) for comparison evolution between hEDS/HSD and CTR group

Table 3: Questionnaires

	hEDS/HSD group		CTR group		P time	P group	P time*group	p η^2
	T1	T2	T1	T2				
Total Baecke	6.9 ± 2.13	7.2 ± 1.24	8.2 ± 1.44	8.6 ± 1.17	0.194	0.001*	0.785	0.001
VAS (/100)	40.8 ± 20.35	45.2 ± 21.65	7.1 ± 13.12	11.2 ± 13.64	0.115	<0.001	0.836	0.000

	hEDS/HSD group		P time	CTR group		P time	P diff	η^2
	T1	T2		T1	T2			
AIMS								
Movement abilities	3.0 [1.5-5.0]	3.0 [1.5-4.1]	1.000	0.0 [0.0-1.3]	0.0 [0.0-0.0]	0.176	1.000	0.009
Walking and bending	6.0 [5.0-8.0]	6.0 [5.0-7.8]	0.778	0.0 [0.0-1.0]	0.0 [0.0-2.0]	0.678	0.308	0.045
Hand and finger function	4.5 [2.0-6.0]	3.2 [2.0-4.5]	0.644	0.0 [0.0-0.0]	0.0 [0.0-0.0]	1.000	0.746	0.017
Arm function	2.5 [0.5-3.6]	1.5 [0.9-2.5]	0.064	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.634	0.332	0.041

Normally distributed data are shown as mean ± SD, non-normal distributed data are shown as median [Q1–Q3]. AIMS: Arthritis Impact Measurement Scales; VAS: Visual Analog Scale; T1 = at baseline (2009); T2 = at follow-up (2017); P time: P value of comparison T2 with T1; P group: hEDS/HSD compared with CTR group; P time*group: P value of comparison evolution between hEDS/HSD and CTR group; P diff: P value of comparison difference scores of T1 and T2 between hEDS/HSD and CTR group; *: P < 0.05; p η^2 : partial eta squared (relative size effect) for comparison evolution between hEDS/HSD and CTR group; η^2 : eta squared (effect size of Mann-Whitney's U test). Higher scores on the AIMS, VAS scale and Baecke Questionnaire indicate higher functional impairment, higher pain levels and higher physical activity respectively.

FIGURE LEGENDS

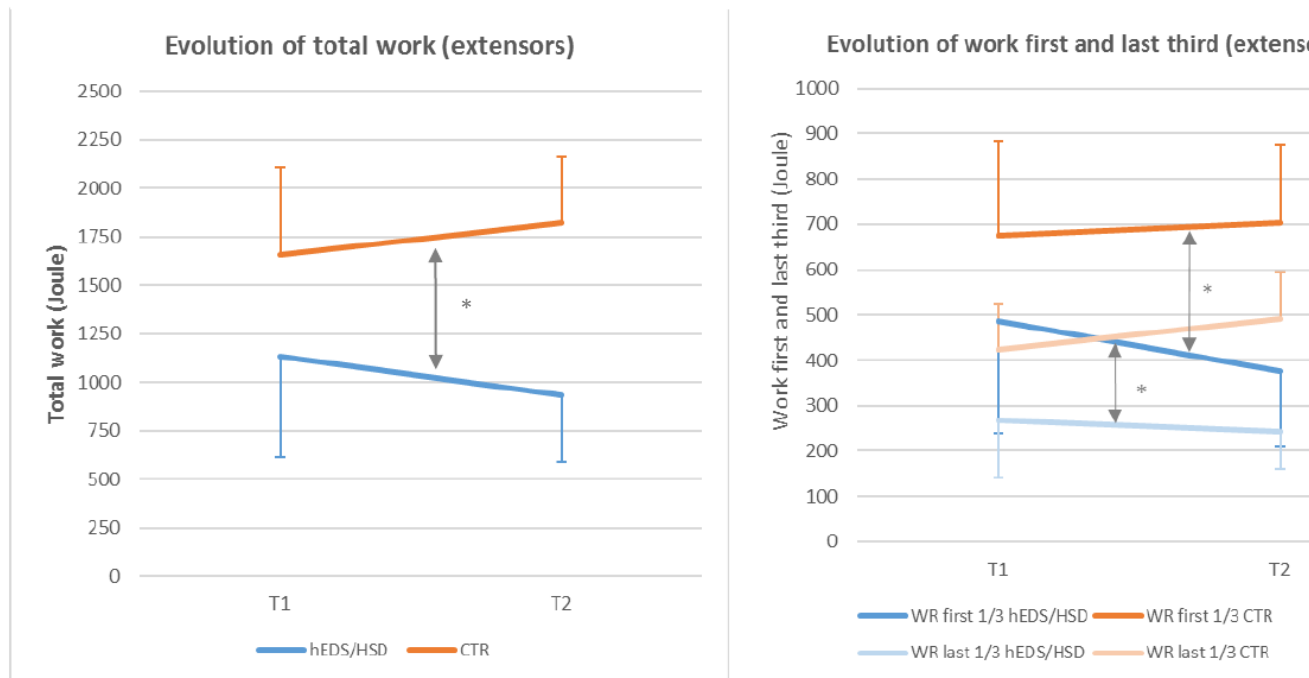
Figure 1: Total work, work first third and work last third for the extensors

T1 = at baseline (2009); T2 = at follow-up (2017); WR first 1/3: work performed in the first third; WR last 1/3: work performed in the last third; hEDS/HSD: patient group; CTR: control group; *: p<0.05

Figure 2: Pain associated with maximal muscle strength and muscle strength endurance tests.

Clustered box plots are shown with medians and interquartile ranges. T1 = at baseline (2009); T2 = at follow-up (2017); VAS = visual analog scale for pain; hEDS/HSD = patient group; CTR = control group; Blue bars = just before the test at baseline; red bars = immediately after the test at baseline; green bars = 1 minute after the test at baseline; orange bars = just before the test at follow-up; yellow bars = immediately after the test at follow-up; light green bars = 1 minute after the test at follow-up; * = outlier

Figure 1: Total work, work first third and work last third for the extensors



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Figure 2: Pain associated with maximal muscle strength and muscle strength endurance tests

