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Impairment and Impact of Pain in Female Patients With Ehlers-Danlos Syndrome

A Comparative Study With Fibromyalgia and Rheumatoid Arthritis

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Objective. **The purpose of this study was to investigate functional impairment and the impact of pain in patients with Ehlers-Danlos syndrome, hypermobility type (EDS-HT), and to compare the burden of disease with that in women with fibromyalgia (FM) and rheumatoid arthritis (RA).**

Methods. **A total of 206 female patients were compared (72 with EDS-HT, 69 with FM, and 65 with RA). Functional impairment was assessed with the Sickness Impact Profile (SIP), and the psychosocial impact of chronic pain was quantified with the Multidimensional Pain Inventory (MPI). Data on symptoms were collected.**

Results. **SIP results showed clinically relevant health-related dysfunction in all groups. Significantly poorer physical, psychosocial, and overall function was found in the EDS-HT group compared with the RA group. In comparison with the FM group, the EDS-HT group reported similar physical and overall function, but better psychosocial function. T scores from the MPI revealed significantly higher levels of pain severity and life interference due to pain, and a lower level of perceived life control, in the EDS-HT group compared to the RA group. In contrast, the EDS-HT group showed significantly lower levels of pain severity, life interference, and affective distress in comparison with the FM group. Social support for help in coping with pain was similar between the 3 groups.**

Conclusion. **EDS-HT is associated with a consistent burden of disease, similar to that of FM and worse than that of RA, as well as a broad impact of chronic pain on daily life, which needs to be addressed in the health care system.**

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of heritable connective tissue disorders, characterized by skin hyperextensibility, tissue fragility, and joint hypermobility (1,2). The hypermobility type is the most common variety of EDS (EDS-HT), representing ~90% of all cases (1). As defined in the Villefranche criteria (1), the dominant clinical manifestation is severe generalized joint hypermobility, which is frequently associated with joint dislocations and joint and limb pain. Musculoskeletal pain in EDS is chronic, severe, and debilitating (3,4). Castori et al recently reported that 3 phases of progression can be recognized in the development of EDS-HT: a hypermobility phase, a pain phase, and a stiffness phase (5). Additionally, fatigue, muscle weakness, and muscle cramps are common associated features (6,7). As such, EDS-HT is considered to be a severe chronic musculoskeletal disorder.

Musculoskeletal disorders require more attention from society and health care systems (8), as these disorders are the most common causes of severe chronic pain and impairment, leading to deterioration in quality of life (9,10). Health-related quality of life (HRQOL) includes physical, emotional, and social function, and how they are affected by health status. Moreover, quality

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of life is an important indicator of disease burden, precisely because it includes the patient's subjective feeling of well-being, satisfaction, function, and impairment. Assessment of HRQOL and identification of factors that reduce HRQOL in EDS-HT are crucial, as this may be a starting point for appropriate symptomatic treatment, which is currently inadequately addressed.

Data regarding the relative health status and impact of pain in different health conditions can be useful in improving health care policy. As EDS is not well known, and is often not identified or taken seriously by medical professionals (11,12), a comparison of the burden of disease between EDS-HT patients and patients with other chronic musculoskeletal conditions, such as rheumatoid arthritis (RA) and fibromyalgia (FM), may put this syndrome in proper perspective.

Both RA and FM display clinical similarities with EDS-HT. RA is a common, severe inflammatory disorder, characterized by progressive joint damage and functional impairment, with common features of daily pain, stiffness, fatigue, and physical disability (13). FM is a common musculoskeletal disorder involving chronic widespread pain and low-threshold tender points (14). Other important symptoms of FM include fatigue, sleep disturbance, morning stiffness, paresthesias, headache, and depression (15). Both RA and FM are well known by health care providers and have been proven to have a negative impact on physical, mental, and social function (16).

The main objective in this study was to investigate functional impairment and impact of pain in female patients who have EDS-HT and to compare the burden of disease with that in women who have FM or RA. This study may thus contribute to a better recognition and understanding of EDS-HT, which is necessary for improving diagnosis, therapy, and management of this debilitating, lifelong disorder.

PATIENTS AND METHODS

Patients. This study included patients with EDS-HT, patients with FM, and patients with RA. The study focused primarily on EDS-HT; the FM and RA groups were included for comparison. In total, 206 nonpregnant women participated.

Female patients diagnosed as having EDS-HT were recruited from the Centre of Medical Genetics at Ghent University Hospital. All patients fulfilled the revised Villefranche criteria for classification of EDS-HT (1), i.e., at least 1 of the 2 main criteria (generalized joint hypermobility, skin hyperextensibility/fragility), in combination with at least 1 of the 3 minor criteria (recurring joint dislocations, chronic musculoskeletal pain, family history positive for the disease). Patients with a history of psychiatric disorder or inflammatory rheumatic disease were excluded. Of the 78 EDS-HT patients who consented to participate, 72 returned the questionnaire and were included in the present study.

The FM patients were recruited from the outpatient Department of Physical and Rehabilitation Medicine at Ghent University Hospital. The American College of Rheumatology (ACR) classification criteria for FM (14) were fulfilled by all patients. Patients with other types of severe somatic disease or a history of psychiatric disorder were excluded. Of the 101 FM patients who consented to participate, 69 returned the questionnaire and were included in the present study.

RA patients were recruited from the Department of Rheumatology at Ghent University Hospital. All patients fulfilled the ACR classification criteria for RA (13). Patients with any other inflammatory rheumatic diseases (e.g., psoriatic arthritis, ankylosing spondylitis) or history of psychiatric disorder were excluded. Of the 98 RA patients who consented to participate, 65 returned the questionnaire and were included in the present study.

Data collection. *Demographic and clinical data.* The procedure for data collection was similar for the 3 patient groups. After a routine physician visit in an outpatient department, eligible patients were given written and verbal information about the study. Patients who consented to participate provided written informed consent and received the questionnaires with a stamped return envelope. Data on demographic and clinical variables were recorded at that time. If responses were not returned within 3 weeks, a reminder phone call was made. All returned questionnaires (90% of the EDS-HT group, 68% of the FM group, and 66% of the RA group responded) were complete and were utilized in the current data collection. The study protocol was approved by the Ethics Committee of Ghent University Hospital.

The RA patients were assessed using the Disease Activity Score in 28 joints (DAS28) (17) and Health Assessment Questionnaire (HAQ) (18). The DAS28 evaluates disease activity in RA patients, including tender and swollen joint count, global assessment score, and C-reactive protein levels (17). The joint counts were performed either by a rheumatologist or by a trained study nurse. DAS28 scores >5.1 correspond to high disease activity, scores of 2.6–3.2 correspond to low disease activity, and scores <2.6 correspond to clinical remission.

The HAQ measures self-reported physical disability in RA (18), and is now also used in several other chronic disorders (19). The validated Dutch disability index consists of 20 questions in 8 categories of relevant physical functions (20). The scores in each category range from 0 (without any difficulty) to 3 (unable to do). A mean total score was calculated, with higher scores indicating greater disability.

Type, prevalence, and severity of symptoms. Two open-ended questions regarding type, prevalence, and severity of symptoms were asked of patients in all groups. The first asked what symptoms patients most frequently experienced related to their disease; the second asked which symptoms patients perceived as being the most severe (7). Similar symptoms were combined for analysis.

Functional impairment in daily life. We used a validated Dutch version (for the northern part of Belgium) (21) and French version (for the southern part of Belgium) (22) of the Sickness Impact Profile (SIP) to measure changes of behavior

Table 1. Characteristics of the study populations*

	EDS-HT group (n = 72)	FM group (n = 69)	RA group (n = 65)	*P*, EDS vs. FM/ EDS vs. RA†
Age, mean ± SD years	40.1 ± 11.94	44.3 ± 9.88	54.9 ± 12.12	NS/<0.001
Household characteristics				NS/NS
Living alone	26 (36.1)	21 (30.4)	13 (20.0)	
Living with others	46 (63.9)	48 (69.6)	52 (80.0)	
Highest education level attained				<0.001/<0.001
Primary school/secondary school until age ≤15 years	8 (11.1)	13 (18.8)	28 (43.1)	
Secondary school until age 18 years	17 (23.6)	32 (46.4)	17 (26.2)	
Higher education	47 (65.3)	24 (34.8)	20 (30.8)	
Employment status				<0.001/<0.001
Employed	29 (40.3)	20 (29.0)	19 (29.2)	
Unemployed/retired due to age	14 (19.4)	9 (13.0)	29 (44.6)	
On sick leave/disability pension	29 (40.3)	40 (58.0)	17 (26.2)	
DAS28, mean ± SD	NA	NA	2.6 ± 1.17	NA
HAQ score, mean ± SD	NA	NA	2.2 ± 0.67	NA

* Except where indicated otherwise, values are the number (%) of patients. EDS-HT = Ehlers-Danlos syndrome, hypermobility type; FM = fibromyalgia; RA = rheumatoid arthritis; NS = not significant; DAS28 = Disease Activity Score in 28 joints; NA = not applicable; HAQ = Health Assessment Questionnaire.
† Determined by analysis of variance or chi-square test.

in everyday activities, due to sickness or illness (23). The standardized questionnaire consisted of 136 items grouped into 12 subscales, comprising ambulation, mobility, and body care and movement (the physical dimension); social interaction, communication, alertness, and emotional behavior (the psychosocial dimension); and the independent subscales sleep and rest, eating, work, home management, and recreation and hobbies. A percentage score (0–100) was obtained for each individual subscale, for the 2 dimensions and for the overall SIP. Higher scores indicate more functional impairment. A score of >10 is arbitrarily considered to indicate significant clinical dysfunction, a score of 0–10 indicates slight dysfunction lacking clinical importance, and a score of 0 indicates no dysfunction.

Assessment of pain impact. To assess and quantify the psychosocial impact of chronic pain, Dutch (24) and French (25) versions of the Multidimensional Pain Index (MPI) were used. The MPI has proven reliability and validity in chronic pain populations (24,26). For the purpose of the current study, 5 MPI subscales (28 items) were measured, including pain severity, interference of pain with daily life, perceived life control, affective distress, and social support for help in coping with pain. Responses to each item were scored by the patient on a 7-point numerical scale (0–6). Raw scores were converted to standardized T scores with a normative value of 50 and an SD of 10. Lower scores on pain severity, life interference, and affective distress subscales signified less psychosocial impairment. Conversely, higher scores on perceived life control and social support were desirable and indicated less psychosocial impairment.

Statistical analysis. The data were analyzed using SPSS, version 17.0. Descriptive statistics are shown as the mean ± SD for continuous data and as percentages or absolute frequencies for categorical data. If data were continuous, the 3 study groups were compared by one-way analysis of variance and multivariate analysis of covariance, adjusting for age, education level, household characteristics, and employment status. The Bonferroni adjustment for multiple comparisons was applied. If data were categorical, group proportions were compared by chi-square test or by logistic regression analysis, controlling for the mentioned covariates. Fisher's exact test was performed if a group proportion was equal to 0. *P* values less than 0.05 were considered significant.

RESULTS

Demographic and clinical data. Characteristics of the study populations are shown in Table 1. There were significant differences in age between the 3 patient groups. The EDS-HT group (mean ± SD age 40.1 ± 11.94 years) was significantly younger than the RA group (54.9 ± 12.12 years), but was similar in age compared to the FM group (44.3 ± 9.88 years). The EDS-HT group had a significantly higher education level than the FM and RA groups. There were also differences in employment status; the proportion of patients who were employed was higher in the EDS-HT group, whereas a larger proportion of the RA group received a retirement pension. More than 40% of the EDS-HT and FM patients received a disability pension or sick leave benefits, compared to only 26.2% of the RA patients. No differences were seen in household characteristics. Furthermore, patients in the RA group had low disease activity (DAS28 2.6 ± 1.17), but were considerably physically disabled (HAQ score 2.2 ± 0.67). All RA

Table 2. Type and frequency of symptoms reported by the EDS-HT group as compared to the FM and RA groups*

Symptom	EDS-HT group (n = 72)	FM group (n = 69)	RA group (n = 65)	*P*, EDS vs. FM/ EDS vs. RA†
Pain	100	100	87.1	NS/NS
Joint pain	100	100	87.1	NS/NS
Headache	32.4	76.8	1.6	<0.001/0.018
Muscle pain	26.8	85.7	16.1	<0.001/0.039
Joint dysfunction	88.7	7.2	19.4	<0.001/<0.001
Dislocations and distortions	88.7	0.0	9.7	<0.001/<0.001
Pelvis instability/snapping hip	25.4	0.0	0.0	<0.001/<0.001
Joint locking	9.9	0.0	3.2	<0.013/NS
Joint swelling	5.6	7.2	8.1	NS/NS
Muscular problems	67.6	87.0	62.9	0.002/NS
Muscle cramps	53.5	27.5	21.0	0.004/<0.001
Tendinitis	31.0	4.3	3.2	0.002/0.003
Muscle weakness	23.9	17.4	3.2	NS/0.011
Muscle stiffness	7.0	84.1	62.9	<0.001/<0.001
Skin problems	60.6	8.7	3.2	<0.001/<0.001
Dysautonomia	47.9	56.5	1.6	NS/<0.001
Fatigue	25.4	89.9	4.8	<0.001/0.021
Neurologic problems	16.9	27.5	3.2	NS/0.047
Sleep disturbances	7.0	82.6	0.0	<0.001/NS
Cognitive problems	1.4	44.9	0.0	<0.001/NS
Emotional problems	1.4	47.8	0.0	<0.001/NS

* Values are the percentage of patients. EDS-HT = Ehlers-Danlos syndrome, hypermobility type; FM = fibromyalgia; RA = rheumatoid arthritis; NS = not significant.
† Determined by logistic regression analysis, with adjustment for age, educational status, household characteristics, and employment status, or by Fisher's exact test if group proportion was equal to zero.

patients used disease-modifying antirheumatic drugs (DMARDs), and half of the RA patients (50.7%) were treated with anti–tumor necrosis factor (anti-TNF) agents.

Reported symptoms. Patients' reports of symptoms are summarized in Table 2. All EDS-HT and FM patients and nearly all RA patients (87.1%) in this study reported pain. The 3 patient groups had a similar very frequent presence of joint pain, whereas the presence of muscle pain and headache was significantly higher in the FM group and significantly lower in the RA group, compared with the EDS-HT group. The joint symptoms of interest, especially dislocations/distortions, pelvis instability, and snapping hip, occurred almost exclusively in the EDS-HT group. Muscle symptoms, however, were frequently present in all patient groups. In particular, muscle cramps, muscle weakness, and tendinitis were significantly more common in the EDS-HT group, while the FM and RA patients reported significantly more muscle stiffness.

Furthermore, EDS-HT patients reported significantly more skin problems (e.g., easy bruising and rupture, difficult wound healing, papyrus scars), symptoms of dysautonomia (e.g., lightheadedness, dizziness, [pre]syncope, diarrhea, constipation, gastroparesis), fatigue, and neurologic problems compared to the RA group. In comparison with the FM group, however, the only significant differences experienced by the EDS-HT group were more frequent skin problems and less fatigue. Sleep disturbances and cognitive and emotional problems were similar in the EDS-HT group and RA group, but reported at significantly higher rates by the FM group.

Joint pain was reported as the most severe symptom by 67.6% of the EDS-HT patients, 76.7% of the FM patients, and 69.8% of the RA patients. Joint dislocations in the EDS-HT group (23.9%), fatigue in the FM group (15.0%), and stiffness in the RA group (26.4%) were reported as the second most severe symptom.

Functional impairment. The mean ± SD overall SIP scores were 19.8 ± 11.87 in the EDS-HT group, 22.3 ± 10.44 in the FM group, and 13.5 ± 8.10 in the RA group, which indicated a clinically significant impact of disease on daily life in all groups. The scores on the physical as well as the psychosocial dimension of the SIP both contributed to this impairment in the 3 study

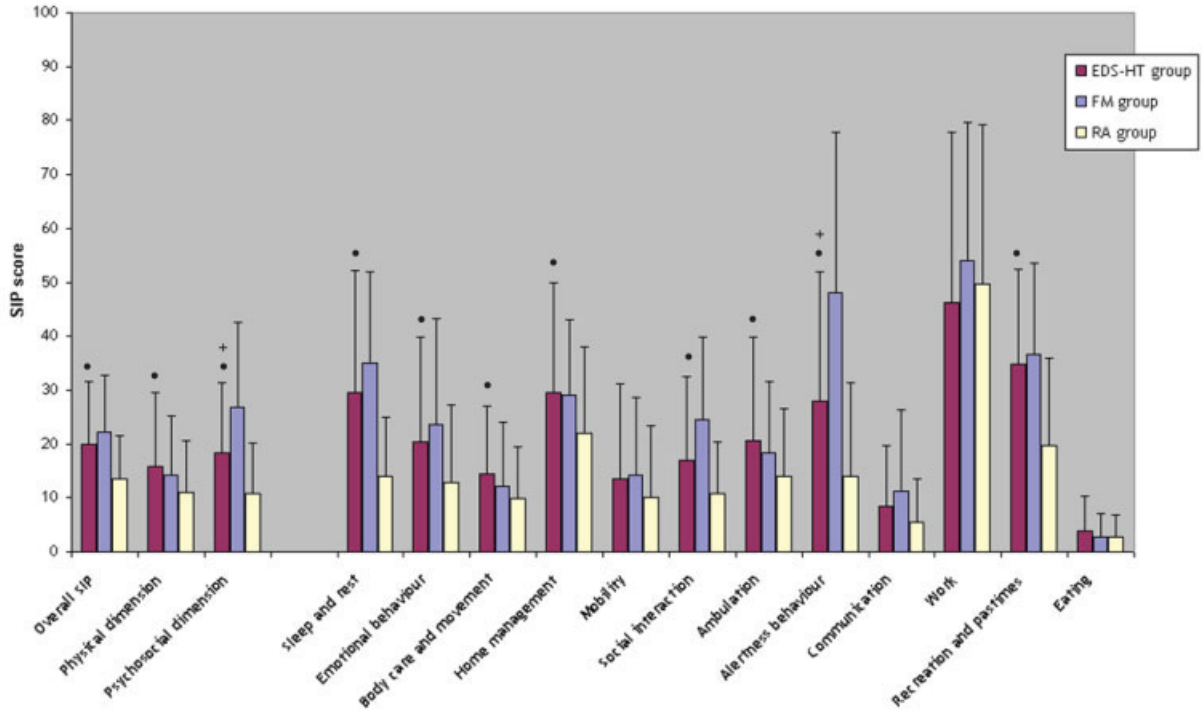

Figure 1. Comparison of functional impairment in daily life in patients with Ehlers-Danlos syndrome, hypermobility type (EDS-HT), fibromyalgia (FM), and rheumatoid arthritis (RA). SIP = Sickness Impact Profile. Values are the mean ± SD. + = $P < 0.05$ versus the FM group; ● = $P < 0.05$ versus the RA group, by analysis of covariance, with adjustment for age, educational status, household characteristics, and employment status.

groups. As illustrated in Figure 1, the EDS-HT group had significantly higher mean SIP scores than the RA group for overall, physical, and psychosocial impairment, whereas the FM group had significantly greater

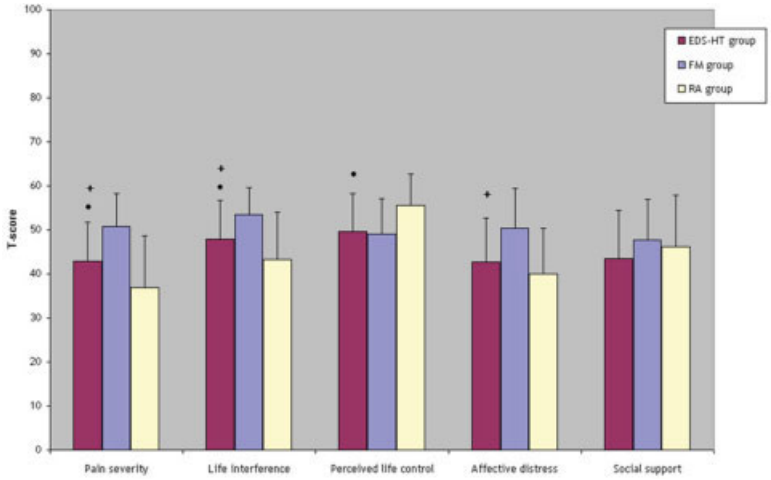

Figure 2. Comparison of pain impact in patients with EDS-HT, FM, and RA. Values are the mean ± SD. + = $P < 0.05$ versus the FM group; ● = $P < 0.05$ versus the RA group, by analysis of covariance, with adjustment for age, educational status, household characteristics, and employment status. See Figure 1 for definitions.

psychosocial impairment in daily life compared to the EDS-HT group.

For all groups, the greatest dysfunction was observed in the subscales of work, recreation and hobbies, home management, sleep and rest, and alertness; the least dysfunction, which lacks clinical importance, was in the subscales eating and communication. Statistically significant differences between EDS-HT patients and RA patients were shown for 8 of the 12 subscales. Differences were especially great in 7 categories: sleep and rest, recreation and hobbies, home management, alertness, emotional behavior, social interaction, and ambulation. The EDS-HT patients scored worse than the RA patients in these areas. When comparing the EDS-HT group with the FM group, only the subscale concerning alertness showed a significant difference between the 2 groups, with the EDS-HT patients having the better score. Functions of eating, communication, and work were similarly impaired in all patient groups.

Impact of pain. The results of this study demonstrated an important impact of pain on daily life for all groups (Figure 2). MPI T scores revealed that the EDS-HT group had significantly higher levels of pain severity, significantly more interference of pain with daily activities, and a significantly lower amount of control over pain and life events compared to the RA group. However, in comparison with the FM group, the EDS-HT group showed significantly lower levels of pain severity and life interference, and had less affective distress (defined as emotional disturbance involving temper, oversensitivity, and anxiety). Social support of significant others for help in coping with pain was similar between the 3 groups.

DISCUSSION

This study shows the presence of severe overlapping features of chronic widespread pain and muscular problems, as well as prominent disease-specific features, in the EDS-HT, FM, and RA groups. The SIP results revealed clinically relevant impairment in all groups. A significantly higher SIP score was found in the EDS-HT group compared with the RA group regarding overall, physical, and psychosocial impairment. In comparison with the FM group, the EDS-HT group scored similarly in physical function, but displayed less psychosocial impairment in daily life. A considerable psychosocial impact of chronic pain in daily life was illustrated concurrently in all groups. The MPI T scores revealed significantly higher levels of pain severity and life interference due to pain, and a lower level of perceived life control in the EDS-HT group compared to the RA group. In contrast, the EDS-HT group showed significantly lower levels of pain severity, life interference, and affective distress compared to the FM group.

The response rates in this study were 90% in the EDS-HT group, 68% in the FM group, and 66% in the RA group. As the mean response rate among mailed questionnaires published in medical journals is ~60% (27), the response in all patient groups in the current study can be considered successful. In the EDS-HT group, however, the response rate was extremely high. This might be due to the high interest in research among patients with EDS-HT, as they often feel helpless and disregarded by the medical community.

The results of the current study confirm that EDS-HT, FM, and RA are chronic musculoskeletal disorders with several clinical similarities. Pain, especially joint pain, was present and reported as the most severe symptom in all 3 patient groups. It is generally accepted that chronic pain has a large negative impact on quality of life, as was also evidenced by the present results. The present study revealed the frequent presence of muscular problems in these diseases; muscle cramps, muscle weakness, and tendinitis, however, were reported significantly more often in the EDS-HT group. These results are in accordance with results of a questionnaire study by our group (7), which established important muscular involvement in EDS-HT. In addition, the results of the study by Voermans et al (6) showed evidence of polyneuropathy and mild myopathy in several EDS patients, based on physical and ancillary investigations.

Additionally, the prevalence of autonomic symptoms was high and of similar magnitude in the EDS-HT and FM groups. Consistent with these results, we recently found that autonomic symptoms were prevalent in 58% of EDS-HT patients, and that these important symptoms have a considerable impact on daily life and pain experience (De Wandele I, et al: unpublished observations).

Further, Voermans et al demonstrated that more than three-quarters of EDS patients experience severe fatigue (28). However, only 25.4% of the EDS-HT group reported fatigue as a frequent symptom in the current study, and just 7.0% reported sleep disturbances, in contrast to the conclusions of Verbraecken et al, who determined that sleep problems (e.g., initiating and maintaining sleep) occurred in 50% of the EDS patients (29). The differences in these results could be due to the differences between the method of self-reporting used in the current study and the standardized questionnaire

used by Voermans et al and Verbraecken et al. In addition, those studies were performed on members of the national patient support group, which introduced a selection bias. The various types of EDS included in the other studies could also explain this large difference in the amount of reported fatigue.

Overall, taking into account all types and frequencies of symptoms reported by patients in the EDS-HT group, it appears that the pain phase of disease progression was predominant in this cohort. According to the 3 phases described by Castori et al (5), the development of EDS-HT includes a hypermobility phase, a pain phase, and a stiffness phase.

With the exception of the extremely low rate of fatigue reported in the RA group (4.8%) in the current study, the prevalence of the most common features in both comparison groups, FM and RA, are in accordance with what would be expected based on most other reports (13–15,30). However, in a study by Repping-Wuts et al (31) severe fatigue was experienced by as many as 50% of the RA patients.

The current results reveal a variety of symptoms present in varying degrees, all of which have a considerable impact on functionality in all 3 patient groups. The SIP results in our study show clinically relevant health-related dysfunction in all groups. In accordance with several previous studies (16,32–36), both RA and FM have a proven major influence on physical, mental, and social daily function. A substantial impact in terms of physical, psychosocial, and independent SIP subscale scores was found in the EDS-HT group. The findings of physical impairment correspond closely with those obtained by Stanitski et al, who reported functional disabilities, such as limited walking, problems with stair climbing, and reduced upper extremity function, in EDS patients (37). Although recurrent joint dislocations, secondary inflammation, and muscular problems result in deterioration of physical function, cognitive problems can also influence all health status parameters, including physical function. In addition, the psychosocial function appeared to be highly deteriorated in EDS-HT patients in our study, in accordance with previous observations of increased rates of anxiety, depression, anger, and interpersonal concerns in patients with EDS (11,38).

Despite the fact that EDS-HT is a debilitating chronic disease and that patients with EDS-HT experience symptoms that are somewhat similar to those of RA and FM, the impact of EDS-HT on daily function has not been well studied. To our knowledge, only a few studies used the SIP to evaluate functional impairment in daily life in EDS patients (28,39). The EDS-HT patients in our study scored worse in all 12 individual domains, as well as in overall function, compared to the EDS patients in the study by Berglund and Nordstrom (mean ± SD SIP score for overall function 19.8 ± 11.87 versus 13.9 ± 12.2, respectively) (39). Possible explanations for these conflicting results include the cultural differences between countries concerning HRQOL (40) and the difference in selection of cases. Specifically, only 30% of the EDS patients in Berglund and Nordstrom's study had the hypermobility type, which is the most debilitating form of EDS with regard to musculoskeletal function (37).

The MPI T scores revealed a considerable psychosocial impact of chronic pain on daily life in all groups in our study. As mentioned above, it is generally accepted that symptoms of pain strongly affect chronic disease patients. Our results confirm that severe chronic pain in all EDS-HT patients in the current study contributes to a large extent to functional impairment in daily life. This is consistent with the findings of Sacheti et al, who reported that chronic pain in EDS affects daily function (i.e., sleep, physical activity, work, social relations, and sexual activity) (3). In addition, Voermans et al recently showed that pain in EDS is related to hypermobility, dislocations, previous surgery, and moderate to severe impairment in daily function (4).

Regarding the comparison of functional impairment between the EDS-HT group and the RA group, the results of the current study clearly show that the EDS-HT patients were more affected by disease in terms of overall, physical, and psychosocial function, as well as on 8 subscales of the SIP. The consistency of differences between these 2 groups supports the robustness of these findings.

The significantly higher impact of pain (as measured by the MPI), expressed as the higher pain severity and interference of pain in daily life, and the lower control over pain in the EDS-HT group compared to the RA group are plausible reasons for these differences in daily function. We therefore would argue that pain management should be a prominent aspect of treatment of patients with EDS-HT, as pain reduction would most likely substantially improve their functional abilities and HRQOL.

Another possible explanation is the fact that diagnosis of EDS-HT is based upon clinical diagnostic criteria alone and is not supported by biochemical or genetic studies, which make EDS-HT and benign joint hypermobility syndrome indistinguishable from each other as they represent the same phenotypic group of patients (41). The complexity of the disease itself, the

use of different diagnostic labels, and the inadequate education of health care professionals regarding EDS-HT may contribute to poorer functional status in patients with EDS-HT compared to patients with RA. Furthermore, treatment in EDS-HT is often not very successful (11,12). In contrast, RA patients have a well-defined disease diagnosis, a better understanding of their disease, and a goal-oriented therapy. As such, effective drug therapy including DMARDs, anti-TNF agents, and other agents in our RA group is reflected in the low disease activity status of the RA patients (mean ± SD DAS28 2.6 ± 1.17). In addition, many EDS-HT patients experience delayed diagnosis and misdiagnosis (5,11,12,42), which often results in inappropriate treatment, unnecessary worsening of the disease, and, consequently, further deterioration in daily function and HRQOL.

A similar reduced overall and physical function, as well as a similar score for almost every subscale, was observed when comparing daily function between the EDS-HT group and the FM group. This similarity between the EDS patients and the FM patients in level of disability was striking, and may increase understanding of the type of impairment experienced by patients with EDS. However, the EDS-HT group had less psychosocial impairment than the FM group, mainly due to differences in alertness. The more frequently self-reported symptoms of fatigue, sleep disturbances, cognitive problems, and emotional problems (e.g., depression) in patients with FM compared to those with EDS-HT may play a role in this finding. In addition, the EDS-HT group had significantly lower levels of pain severity and life interference, and had less affective distress (defined as emotional disturbance involving temper, oversensitivity, and anxiety) compared with the FM group. This higher level of distress in FM may contribute to an increase in the severity of daily stressors, thereby influencing patient perception of health.

Our results must be viewed within the limitations of the study. These findings cannot be extrapolated to all patients with EDS-HT, because the patients recruited for our study had been referred to the outpatient department of Ghent University Hospital, and thus probably had more severe disease than a random sample of patients with EDS-HT. In addition, for the comparative analyses we selected patients with FM and RA who also had been recruited at an outpatient department of Ghent University Hospital. Another study limitation is the inclusion of only female patients. However, 90% of EDS-HT patients (1), 90% of FM patients (43), and 66% of RA patients (44) are women. Furthermore, we used nonspecific, open-ended questions to list and compare the type and prevalence of symptoms among the 3 patient groups. Open-ended questions are not a substitute for standardized questionnaires. Due to this self-report method, our results could underestimate the real proportion of symptoms. However, we can assume that our results identify those symptoms that are of importance to the patient, and therefore these results can be used as a reference in creating standardized questionnaires for future studies in this population.

Despite these limitations, our results emphasize that EDS-HT is associated with a consistent burden of disease, similar to or worse than FM or RA, respectively, as well as a broad impact of chronic pain on daily life. Little is known about the disease, and no effective treatments are currently available for patients with EDS-HT. Consequently, health care professionals should use current understanding to more accurately establish diagnoses of EDS-HT, and future research should focus on the development of adequate multidisciplinary management of this disorder, including pain management, physiotherapy, and psychological followup.

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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. Dr. 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.

Study conception and design. Rombaut, Malfait, De Paepe, Rimbaut, Verbruggen, De Wandele, Calders.

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