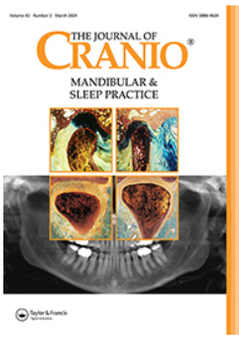

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Treatments related to temporomandibular disorders among patients with prevalent types of Ehlers-Danlos syndrome in Sweden

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ABSTRACT

The aim of this study was to assess the received TMD treatment modalities and the perceived outcome among the frequent types of EDS. A digital questionnaire was sent to the member of the National Swedish EDS Association during January-March 2022. The subsamples of hypermobile and classical EDS were constructed. Almost 90% reported TMD symptoms. Bite splint therapy, counselling, jaw training and occlusal adjustment were reported as the most common treatments with no statistically significant difference in terms of good effect between the two subsamples. Hypermobile and classical EDS might consider as an entity with regards to TMD.

KEYWORDS

Temporomandibular disorders; Ehlers-Danlos syndrome; hypermobility; splint therapy; jaw exercises; occlusal adjustment; counselling

Introduction

Temporomandibular disorders (TMD) is a common condition among adults. TMD describes a number of painful and non-painful disorders affecting the jaw muscles, the temporomandibular joint (TMJ), and associated structures [1]. It is considered the most common cause of nondental orofacial pain with a prevalence of 5 to 12% [2], and is the second most common musculoskeletal condition [3]. The aetiology of TMD is considered multifactorial comprising biological, psychological and social factors [4]. The normal function of the TMJ may be influenced by generalized joint hypermobility (GJH), which is a featured characteristic of Ehlers-Danlos Syndromes (EDS) [5–7].

EDS is a heterogeneous group of inherited connective tissue disorders characterized by joint hypermobility and cutaneous hyperextensibility and fragility. The current EDS classification distinguishes 13 different EDS types resulting from mutations in either collagen-encoding genes or in genes encoding collagen modifying enzymes [8]. Clinical manifestations of the syndrome vary depending on the EDS subtype and the underlying genetic defect [8].

The prevalence of EDS has been estimated to impact roughly 1:2.500 to 5.000 births [9]. The most common type is hypermobile EDS (hEDS) with a prevalence of between 1:5.000 and 1:20.000, followed by classic EDS (cEDS) at 1:30.000 and vascular type EDS (vEDS) at 1:90.000. The prevalence for the some rare types such as periodontal EDS (pEDS) is still unknown [10].

The diagnosis of hEDS requires the simultaneous presence of several strict criteria as follows: generalized joint hypermobility, evidence of specific syndromic features, musculoskeletal manifestations, and family history [8]. Individuals with joint hypermobility and musculoskeletal manifestations that do not fulfil criteria for hEDS are diagnosed as hypermobility spectrum disorder (HSD) [11]. cEDS is defined by skin hyperextensibility and atrophic scarring as well as generalized joint hypermobility and several minor criteria [8].

Symptoms indicative of TMD are reported more often among individuals with EDS compared to the general population; this is presumed to be linked to TMJ hypermobility as a part of generalized joint hypermobility [6,12,13]. TMJ dysfunction symptoms such as hypermobile joints during extreme mouth opening, jaw locking when biting into thick food, clicking, crepitation and permanent jaw lock are common among EDS patients [14]. TMJ dysfunction is suggested to be associated with TMJ disc and abnormalities of the capsular ligamentous attachments [15]. The TMJ can relocate again after a hyperextension, but this may induce a disc displacement pain and dysfunction such as limited jaw mobility [16]. High frequency and long duration of TMJ dislocations can lead to a high chronic pain score [13]. Masticatory muscle pain may cause lower functionality and quality of life among those affected [17,18]. Spinal posture and cervical function

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of the head and neck have also been proposed as important contributing factors for TMD among EDS patients [16,19].

Despite the fact of EDS being a risk factor for TMD, lack of diagnosis, inadequate care, and being accused for malingering have been reported as reasons why patients feel defeated and have negative impressions toward dental care and health care systems [20–22]. Therefore, the prevalence of TMD as well as the treatment need for TMD among individuals with EDS are still unknown.

The first aim of this study was to identify socio-demographic, socio-economic, health-related and psychological factors among EDS/HSD sample. An additional aim was to assess the most bothersome self-reported pain region in the body, TMD symptoms prevalence, the received TMD treatment modalities and the perceived outcome of those modalities among frequent types of EDS in Sweden.

Material and methods

Study design

This study was designed as a questionnaire-based cross-sectional study of an EDS population in Sweden. Members in the National EDS Association were approached who had confirmed EDS diagnosis or were under investigation for EDS in the health care system. The study was performed in accordance with the ethical principles for medical research involving human subjects according to the World Medical Association Declaration of Helsinki. Written information about the purpose of the study was provided and informed consent was obtained from all participants. The study was approved by the Ethics Committee Dnr 2021–05840–01. To participate in this study, participants had to give a positive response to two questions – if they had received enough information regarding the study, and if they consented to participate in the study. Data were collected January-March 2022.

Questionnaire

A digital questionnaire consisting of 63 validated questions including EDS type, socio-demographic factors, socio-economic factors, health-related factors, physiological factors, pain pattern, self-reported TMD symptoms and its treatment modalities was sent to participants' email addresses via a digital link.

Measurements

Patient health questionnaire (PHQ-4) is an instrument with four questions that screen for distress as the composite construct of anxiety and depression. The total score is the sum of four item scores. The scores are rated as normal (0–2), mild (3,4,5), moderate (6,7,8), and severe (9,10,11,12) [23].

Self-reported TMD symptoms are defined as *pain* – reported headache or feel pain, stiffness or fatigue in jaws with waking up in the morning, and *dysfunction* – luxation, clicking or crepitation. To identify individuals with possible TMD, the 3Q/TMD was used as three screening questions for TMD [24]. Question 1 (Q1) asks about pain in the temple, face, TMJ or jaw once a week or more often. Question 2 (Q2) asks about pain with opening the mouth wide or chewing once a week or more often. Question 3 (Q3) asks about whether the jaw locks or becomes stuck once a week or more often.

Participants

Individuals who were invited to participate in this study were those aged 16 years and older who had a confirmed diagnosis of EDS or were under diagnosis for EDS and were members of the National EDS Association in Sweden. The number of members (both patients and non-patients) in the association were 1431 individuals, of which, 1393 were women, 134 were men, three were other (not man or woman), and one member did not mention his/her sex.

In total, 279 individuals sent back the digital questionnaire. We excluded those who had not yet been diagnosed with EDS ($n = 19$), who had incompletely filled out the questionnaire ($n = 28$), and who had repeatedly filled out the questionnaire ($n = 9$). This resulted in a total cohort of 223 participants with a confirmed diagnosis. Those with HSD and hEDS were considered as one group (HSD/hEDS) ($n = 152$) due to the overlapping of the clinical features [8]. The rest of the participants were those with other subtypes as follows: cEDS ($n = 31$), vEDS ($n = 4$), pEDS ($n = 2$) and those not knowing their type of EDS ($n = 34$) (Figure 1).

Statistical analysis

Data analysis was carried out using STATA version 14. The total sample ($n = 223$) was described by descriptive statistics in terms of absolute numbers and prevalence figures. The prevalence of TMD, the self-reported most bothersome pain, as well as the received treatments related to TMD and the subjective good effect of those treatments were presented for the HSD/hEDS ($n = 152$) and cEDS ($n = 31$) groups. To compare proportions, the

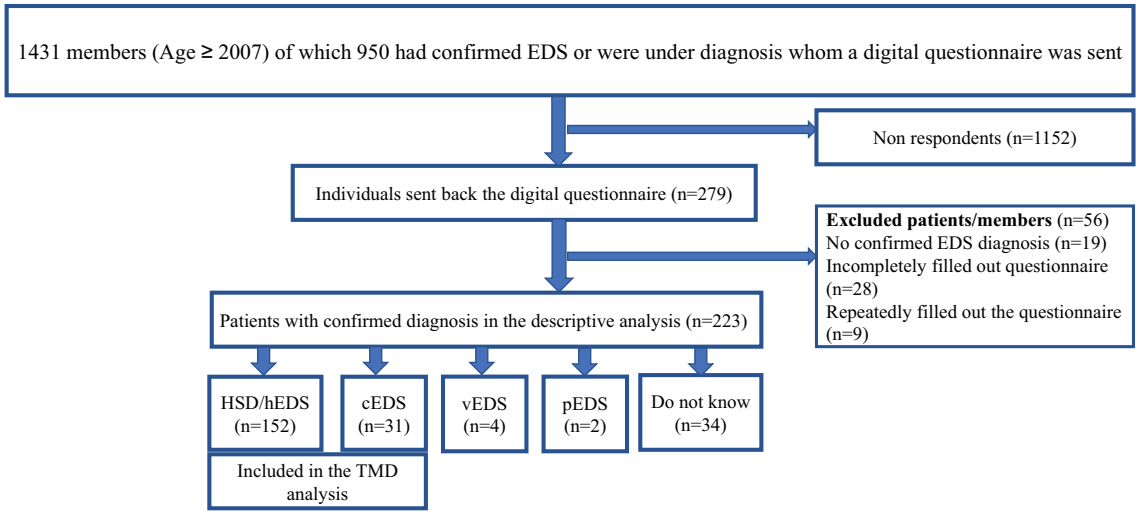

Figure 1. Inclusion and exclusion of participants in this study. EDS, Ehlers-Danlos syndrome; HSD/hEDS, hypermobile spectrum disorder/hypermobile EDS; cEDS, classical EDS; vEDS, vascular EDS; pEDS, periodontal EDS. Do not know the type of EDS.

Chi-square test and Fisher's exact test were used when it was applicable. The significance level was set at $p < .05$.

Results

Table 1 represents the characteristics of the sample with confirmed EDS/HSD diagnosis ($n = 223$). The mean age of the sample was 49.24 ± 26.04 years. Women constituted 95% of the sample. Most of the participants were not working (54%). Overall, 91% of the participants reported poor general health, and 42% reported poor oral health. More than half of the sample (55%) were overweight and obese. Nearly 16% reported a diagnosis with autistic disorders. The majority (70%) reported mood disturbances such as anxiety or depression.

Table 2 presents comparison of the symptoms indicative of TMD among those with HSD/hEDS ($n = 152$) and with cEDS ($n = 31$). The results were not statistically significant between these two subsamples. Most of the participants responded affirmatively to the 3Q/TMD as well as the self-reported TMD symptoms. Nearly 45% of the HSD/hEDS participants reported an uncomfortable occlusion compared to 39% of the cEDS participants.

Pain pattern among HSD/hEDS and cEDS

Patterns of the most bothersome self-reported pain region among the HSD/hEDS ($n = 152$) and cEDS ($n = 31$) participants are presented in the Figure 2. Among the HSD/hEDS, the proportions of the worst pain were reported as follow: head, neck and lower back (12%), hip (11%), shoulders, belly and knee (9%), jaw (8%), wrist (7%), foot joints (5%), feet (4%), and chest and elbow (3%). Among the cEDS, the proportions of the worst pain were reported as follow: lower back (19%), belly, chest, neck (10%), head, jaw, knee, and hip (6%), elbow, and foot joints and feet (3%). The pain patterns were not statistically significant between groups.

Treatments related to TMD among cEDS and HSD/hEDS

Overall, 94% of the cEDS ($n = 31$) and 80% of the HSD/hEDS ($n = 152$) participants had demanded treatment for TMD from dentists, doctors, physiotherapists, osteopaths, chiropractors, and others (orthodontist, TMD specialist, dental hygienist, and hospital nurse). Eighty-one percent of the cEDS participants with TMD had demanded treatment from dentists (including dental specialists), while the respective proportion was 66% for the HSD/hEDS participants. Overall, 64% of the cEDS and 67% of the HSD/hEDS participants reported that they experienced that the dental staff did not have adequate knowledge regarding EDS to provide them with good dental care; there was no statistically significant difference between the two subsamples (data not shown here).

Figure 3 presents the received treatment modalities for TMD as well as the good subjective effect of those treatments among the HSD/hEDS ($n = 152$) and cEDS ($n = 31$) groups. The majority had received bite splint therapy, counselling, jaw exercises, occlusal adjustment or orthodontic treatment. Around 3% of the HSD/hEDS group received Botox injection compared to 16% among the cEDS group. The results were statically significant in

Table 1. Descriptive statistics of the participants with confirmed diagnosis of EDS/HSD ($n = 223$).

Variables	Definition	n	(%)
Socio-demographic factors			
Gender	Self-reported gender		
Women		212	(95)
Men		6	(3)
Other		5	(2)
Age	Self-reported age in year		
Mean (SD)	49.24 (26.04)		
Living condition			
With other	Married, cohabiting, living with parents	157	(70)
Alone	Divorced, separated, widow, widower	66	(30)
Socio-economic factors			
Education			
Primary	Elementary	11	(5)
Secondary	High school & qualified vocational training	100	(45)
University	University/college	112	(50)
Employment status			
Working		101	(46)
Not working	Studying, retirement (early & normal age), unemployed, parents leave, sick leave, housewife/man	119	(54)
Sick leave	The days away from the work in the last 12 months		
No days		114	(59)
7–30 days		41	(21)
31 days or more		38	(20)
Saving of 20,000 SEK	Able to pay 20,000 SEK within a month without borrowing		
Yes		143	(64)
No		79	(36)
Health-related factors			
Self-perceived general health			
Good	Very good, good	20	(9)
Poor	Moderate, poor, very poor	203	(91)
Body Mass Index (BMI)	Weight (kilograms) divided by the square of the height (meter)		
Underweight	BMI <18.5	7	(3)
Normal	BMI 18.5–24.5	91	(42)
Overweight	BMI 25–29.9	54	(24)
Obesity	BMI ≥30	69	(31)
Smoking cigarette/snuff			
No	No/stopped	149	(67)
Yes		72	(33)
Self-perceived Oral health			
Good	Very good, good	128	(58)
Poor	Moderate, poor, very poor	95	(42)
Number of Teeth			
25–32		178	(80)
0–24		45	(20)
Dental fear (phobia)	Afraid of dental care		
No		157	(71)
Yes		65	(29)
Psychological factors			
Patient Health Questionnaire	Composite construct of anxiety and depression		
Normal	0–2 points	91	(41)
Mild	3–5 points	76	(34)
Moderate	6–8 points	34	(15)
Severe	9–12 points	22	(10)
Autistic Spectrum disorders (ASD)	A diagnosis in the field of autism spectrum		
No	No/do not know	186	(83)
Yes		35	(16)

terms of counselling ($p = .04$) and occlusal adjustment ($p = .02$) between the HSD/hEDS and cEDS. Due to too small samples, proportions of other treatment modalities were not compared among groups.

Overall, 57% of the HSD/hEDS and 61% of the cEDS groups reported good effects for the received treatments. The high proportions were related to bite splint therapy, jaw training, occlusal adjustment, counselling, and orthodontic treatment, with no statistically significant difference between the two groups. Further, the subjective good effect of Botox injection was not statistically significant between the groups.

Table 2. Symptoms indicative of temporomandibular disorders (TMD) among those with HSD/hEDS ($n = 152$) and with cEDS ($n = 31$).

Variables	*Definition*	*HSD/hEDS n (%)*	*cEDS n (%)*
Screening 3Q/TMD			
Q1	Affirmative response to pain in the temple, face, TMJ or jaw once a week or more	125 (82)	26 (84)
Q2	Affirmative response to pain in the temple, face, TMJ or jaw during jaw functions once a week or more	113 (74)	27 (87)
Q3	Affirmative response to jaw locking/impaired jaw opening once a week or more	73 (48)	18 (58)
Self-reported TMD pain	Headache/Feel pain, stiffness, or fatigue in the jaws with waking up in the morning	145 (95)	28 (90)
Self-reported TM dysfunction	luxation/clicking/crepitation	135 (89)	30 (97)
Self-reported uncomfortable occlusion	Teeth do not fit together	68 (45)	12 (39)
Parafunction habits	Bruxism/tongue pressing/biting cheeks or lips	143 (94)	30 (97)

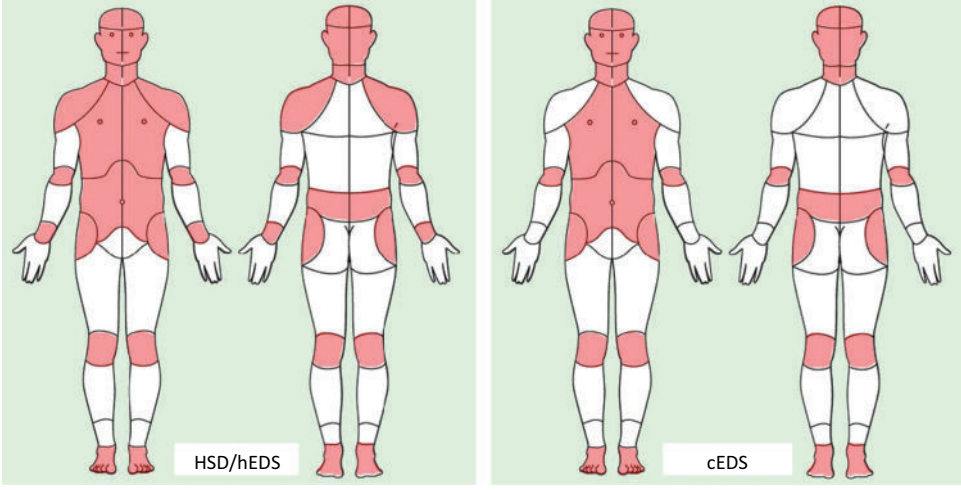

Figure 2. Illustration of the most bothersome self-reported pain patterns among HSD/hEDS (n=152), and cEDS (n=31) groups. Pain in the head and neck is illustrated in both front and back views; pain in the jaw is illustrated as pain in the face; pain in the foot joints and feet is illustrated in the same location.

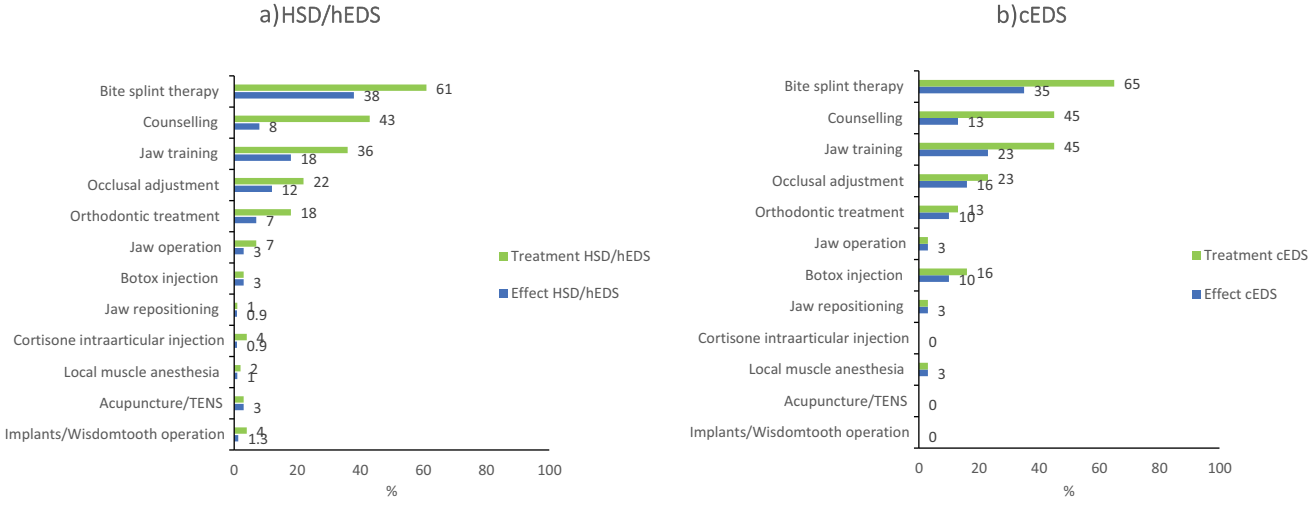

Figure 3. Different treatment modalities for TMD and Good subjective effect of the received treatments among A) HSD/hEDS (n=152), and B) cEDS (n=31).

Discussion

In the present questionnaire-based study, nearly all participants from the National EDS Swedish Association with confirmed EDS reported symptoms known to be indicative of TMD. The prevalence of TMD symptoms and the pattern of the most bothersome pain in the body were similar among the HSD/hEDS and cEDS groups, except for pain in the shoulder and wrist regions. The most common treatments related to TMD in both groups were bite splint therapy, counselling, jaw training, occlusal adjustment and orthodontic treatment. The subjective good effect of these treatment modalities was not statistically significant between the two groups.

Socio-demographic, health-related and psychological factors among EDS participants

As expected, most of the respondents were women [25–27]. The number of women in the National EDS association in Sweden is dominant, and the same pattern was reported in a Swedish study 2001 [12]. Compared to men, women are generally more hypermobile and experience higher pain intensity and joint complications, which results in them actively seeking treatment [28]. The role of testosterone with an antinociceptive function [29] as well as fluctuation of sex hormones in females as a factor with an impact on symptomatology and clinical evolution of hEDS have been discussed [30]. More susceptibility to a genetic predisposition for hEDS among the female foetus has been claimed [31], which is against an autosomal dominant trait of this diagnosis.

In the present study, the mean age of the participants was approximately 50 years, the majority was not working, and a significant proportion had retired early. In a previous Swedish study among EDS with a mean age of 39 years, more than 50% worked part-time or had disability pension or sick leave benefits, which indicates that they were more dysfunctional compared to those who worked full-time. Moreover, higher scores on were reported the Sickness Impact Profile index among the EDS compared to the general population [12]. The self-reported poor general health by almost 91% in our sample reflects an impaired functional health. Disruption of education or employment was also reported as a detrimental factor for health and wellbeing [32].

More than half of the sample reported high BMI that reflects overweight and obesity. Among the EDS, significant disability not only in daily living activities (personal hygiene-self-care) but also in ambulation (walking, running, stair climbing) and sport activities has been reported [18,33]. General hypermobility (joint instability and excessive joint motion) [28] and painful subluxation and dislocation [33] as well as chronic fatigue [32] are among the most common causes for poor physical activity and disability [34]. Chronic fatigue as a common symptom among the EDS can be due to poor sleep quality, frequent pain, dysautonomia, or to depression or anxiety [32]. In our study, nearly 80% reported fatigue and poor sleep quality.

Fifty-eight percent of the EDS group experienced good oral health; however, 30% reported dental fear and 20% reported partial or total edentulism. General population-based studies in Sweden among adults found lower education level and socio-economic position associated with fewer remaining teeth, more oral diseases (caries and periodontitis) and a refrainment from dental care [35,36]. The majority in our EDS group had a high education level, were cohabitating, and were able to pay 20.000 SEK within a month without borrowing; this indicates that other factors might have contributed to the self-reported poor oral health among the EDS. Currently, there is no reliable evidence for an increased periodontitis risk associated with EDS, except for the periodontal EDS [10]. However, EDS-specific oral manifestations [37] including abnormal dentition [15,38] were reported previously. Based on the recent retrospective survey among both the EDS and non-EDS who had undergone a dental procedure, EDS respondents recalled three times more inadequate pain prevention compared to non-EDS respondents [39]. The mechanism for local anaesthetic resistance is not known [40], but experiencing pain during dental procedures can be traumatic, and may result in refraining from dental care. Generally, dental fear creates a vicious cycle through avoidance behaviour and deterioration in dental status, which in turn results in feeling of shame and more anxiety [41].

Mood disturbance such as anxiety or depression was common in our EDS sample as was the case in previous studies [27,42]. A large-scale study in Sweden reported a higher risk of mood and development disorders among the EDS compared to the general population [43]. Among the EDS, progression of the symptoms [22] as well as incomprehension regarding physical restriction and social disability with surroundings resulted in anxiety and enhanced somatisation [44]. Depressive symptoms can either be due to frequent pain or as a cause of pain [45,46]. In our sample, 16% reported autistic spectrum disorders (ASD), which reflects the association between ASD and EDS [43,47]. However, the cause for ASD among EDS is unclear [48].

HSD/hEDS & cEDS

In the present study, participants reported their confirmed type of EDS based on phenotype manifestations. Clinical distinction between the prevalent types of EDS that include hEDS and cEDS has been a challenge and sometimes very difficult [49]. A mild presentation of cEDS may be mistaken for hEDS; this includes similar degrees of joint laxity, pain, and other manifestations including dental system. The diagnosis may be revised from hypermobile to classic when the individual's later development trends more towards cEDS, i.e. significant skin and soft tissue manifestations. In some cases with hEDS, a definitive genetic mutation on Tenascin XB has been found that manifests symptoms similar to cEDS [50]. However, there is no confirmation genetic test regarding hEDS; thus, the new EDS classification system in 2017 purposed to identify hEDS with a higher precision clinically. Moreover, the Beighton index was standardized to increase reliability and decrease inconsistency within the health care [8]. Nevertheless, the clinical usefulness and productive validity of the Beighton index as well as the shortcoming of the new classification system have been highlighted in some studies [51,52]. In addition, HSD as conditions presenting with symptomatic joint hypermobility, but not matching the hEDS diagnostic criteria [11], should be considered as a phenotypic entity with hEDS [8]. Taken together, there might be misdiagnoses of HSD/hEDS and cEDS in our study.

On the other hand, TMD manifestation depends on the affected collagen types I, III, V, in the TMJ structure among those with EDS [53]. Therefore, one suggestion is to consider HSD/hEDS and cEDS as one entity in terms of TMD symptoms, as reflected in our findings. Further investigation is highly recommended.

TMD among HSD/hEDS & cEDS

Most of both subsamples had an affirmative response to the 3Q/TMD (i.e. higher prevalence for frequent pain – Q1& Q2, in comparison to frequent dysfunction – Q3). Approximately 90% of the subsamples reported symptoms indicative of TMD. Previous studies assessed TMD in small sample sizes and in mixed EDS subgroups [13,54,55], or solely among hEDS patients [56,57]. The prevalence of TMD pain among EDS has been estimated at 40–100% [58], which is in line with our findings. Nevertheless, a direct comparison is not plausible since those who had TMD participated in this study, thus reflecting the high prevalence figures for TMD pain and dysfunction. In a recent study in Denmark among 26 hEDS patients (mean age: 34.5 years ±10.01 years), a higher prevalence of myofascial pain with referral was registered in comparison to healthy controls [57]. In a study among 18 hEDS females, 100% reported pain, 33% reported clicking and locking, and 40% reported dislocation and trismus [59]. TMJ dislocation may be the result of a physical jamming of the disc-condyle complex beyond the articular eminence, i.e. maintained by muscle activity or a true hyperextension of the disc-condyle complex beyond its normal translation position [60]. Craniocervical instability can also result in TMJ subluxation through overuse of mastication muscles [19].

Pain pattern among HSD/hEDS & cEDS

Our findings confirm musculoskeletal pain patterns among the most frequent types of EDS as other studies [26,61–63], although with lower prevalence figures. This is possibly due to the wording of the question asking about the most bothersome region and that we presented the prevalence figures separately in each subsample. Lower back pain was the most bothersome pain region in both subsamples. Among the EDS, abnormalities in the vertebral shape [64], poor postural control due to chronic joint instability, and degenerative disease as a consequence of increasing of the mechanical stress in the joint's surfaces [63] might be reasons for such a pattern. In that previous study, the cEDS did not report shoulder or wrist pain as the most bothersome pain regions compared to the HSD/hEDS even though the difference was not statistically significant. A higher prevalence of shoulder dislocation was previously reported among HSD patients [65]. Headache as a common symptom among EDS has heterogeneous mechanisms with wide intraindividual variations [66,67]. Neck pain due to cervical spine hypermobility/dysfunction can also lead to cervicogenic headache [66]. Pain in the belly among the most bothersome regions might be due to gastrointestinal symptoms [68]. Pain in the jaw may reflect comorbidity between pain in the trigeminal area, widespread pain, and as a sign of general hyperalgesia [69–71]. Among the EDS, different underlying mechanisms such as general hyperalgesia [72], neuropathic pain [73], widespread pain [26,61,74] and deficiency in the endogenic system [74] have been proposed for chronic pain.

Taken together, we suggest that TMD among the EDS may be considered as a part of the chronic musculoskeletal pain that requires a treatment plan with a multidisciplinary approach. Previous studies have suggested such an approach including cognitive-behavioural therapy [75–77].

Treatment & effects related to TMD

In Sweden, national guidelines are the reference for the treatments related to TMD [78]; however, there is no

specific guidelines that has been tailored to EDS patients. Based on existing literature, the treatment of TMD among the EDS should be conservative and non-invasive, since open surgery may interfere considerably with the healing process thus leading to increased morbidity and mortality [79]. Conservative treatments may have short-term benefit but for a considerable number of patients may be sufficient to relieve symptoms. Surgical interventions such as arthroscopy in the failure of conservative treatments has been suggested [59], which needs more investigation.

Counselling is the first stage of conservative treatment [78]. However, in our study, there was a rather low subjective good effect of this modality, which might reflect the lack of knowledge and experience within EDS among dental staff as was reported by respondents. Education about EDS and its manifestation such as pain physiology within health care has been strongly recommended previously [80–82].

More than 50% of those who received bite splint therapy reported a good effect. Bite-splint reduces abnormal muscle activity resulting in a neuromuscular balance in the chewing system by providing the ideal centric relation [83]. In our study, the majority of both subsamples reported parafunction behaviours; this contrasts with the result of a study by De Coster PJ et al. who recorded bruxism in 28% of the sample with no association with TMD signs and symptoms [13]. In a prospective cohort study, self-reported bruxism was found as a strong predictor of chronic TMD [84].

Exercise of the jaw-system had a good effect among half of our study population. To our knowledge, there is no study regarding jaw exercises specifically among EDS. Generally, the evidence regarding deficiencies in movement coordination and muscle strength among adults with hEDS or cEDS are from the gait laboratory [85]. Decreasing muscle power can be due to low tendon stiffness as a result of joint hypermobility among those with hEDS and cEDS [86,87], which can interfere with force transmission from muscles to bones, even with normal muscle structure [88]. Thus, activating the muscles has been proposed as a good way to stabilize the joints, albeit with caution. Fatigue [32], fear of movement (kinesiophobia) and getting pain or injury because of exercises among HSD/hEDS patients [63] have been suggested for non-adherence to physical exercises among EDS patients. Thus, learning how to adjust and overcome the kinesiophobia [89] might have a critical role among EDS patients with TMD. Therefore, we strongly recommend jaw exercises under supervision for EDS patients to decrease the risk of trauma to the joints, and also to keep the patients motivated.

Roughly 50% of both subsamples reported good effect of occlusal adjustment. About half of the HSD/hEDS sample and 40% of the cEDS cases reported an uncomfortable occlusion. In a questionnaire-based study among EDS in Germany, 37% reported the jaws not fitting together, which was attributed as dysgnathia [90]. Thus, good effect of orthodontic treatment in our sample might also reflect treatment of malocclusion and not solely TMD. How the occlusal adjustment was done among the EDS needs to be clinically investigated.

The rest of the treatments were reported among very few respondents; this requires further investigation.

Strength & limitation

This is the first epidemiological study assessing the TMD, treatment modalities and the effect of those modalities in quite large subsamples of the prevalent confirmed EDS types in Sweden. A comprehensive questionnaire with validated questions was applied to create a holistic picture regarding TMD among EDS. The response rate to the questionnaire was considerably low. The recruitment of members of the National EDS Association may result in selection bias. There are no data available regarding non-response bias. Thus, the generalizability of our findings should be made with caution since the proportion of the EDS population in our study and the total EDS population in Sweden remains unknown. Overrepresentation of TMD among EDS patients is another limitation of our study. Also, inferring causality was not possible due to the cross-sectional design of the study.

Conclusion

HSD/hEDS and cEDS might be considered as an entity with regards to TMD symptoms. The common conservative treatments related to TMD resulted in subjective good effects among the frequent types of EDS. Education about EDS and its manifestation among dental staff is compulsory in Sweden. There is a compelling need for further research in this area to assure the best possible treatment options among EDS.

Author Contributions

NY and AW developed the research question and designed the study. NY collected the data. NY led the analysis and interpretation of results supported by MN, AW. NY drafted the manuscript which was critically revised by the two co-authors. All authors approved the final version of the

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References

[1] Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 1992;6(4):301–355.
[2] Durham J, Al-Baghdadi M, Baad-Hansen L, et al. Self-management programmes in temporomandibular disorders: results from an international Delphi process. J Oral Rehabil. 2016;43(12):929–36. doi: 10.1111/joor.12448
[3] National Institute of Dental and Craniofacial Research. Facial Pain. Available from https://www.nidcr.nih.gov/research/data-statistics/facial-pain .
[4] Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196 (4286):129–36. doi: 10.1126/science.847460
[5] Hirsch C, John MT, Stang A. Association between generalized joint hypermobility and signs and diagnoses of temporomandibular disorders. Eur J Oral Sci. 2008;116 (6):525–30. doi: 10.1111/j.1600-0722.2008.00581.x
[6] Westling L. Temporomandibular joint dysfunction and systemic joint laxity. Swed Dent J Suppl. 1992;81:1–79.
[7] Tinkle BT. Symptomatic joint hypermobility. Best Pract Res Clin Rheumatol. 2020;34(3):101508. doi: 10.1016/j.berh.2020.101508
[8] Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8–26. doi: 10.1002/ajmg.c.31552
[9] 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. pp. 351–407.
[10] Kapferer-Seebacher I, Lundberg P, Malfait F, et al. Periodontal manifestations of Ehlers-Danlos syndromes: a systematic review. J Clin Periodontol. 2017;44(11):1088–1100. doi: 10.1111/jcpe.12807
[11] Castori M, Tinkle B, Levy H, et al. A framework for the classification of joint hypermobility and related conditions. Am J Med Genet C Semin Med Genet. 2017;175(1):148–157. doi: 10.1002/ajmg.c.31539
[12] Berglund B, Nordström G. Symptoms and functional health status of individuals with Ehlers-Danlos syndrome (EDS). J Clin Rheumatol. 2001;7(5):308–314. doi: 10.1097/00124743-200110000-00010
[13] De Coster PJ, Martens LC, De Paepe A. Oral health in prevalent types of Ehlers-Danlos syndromes. J Oral Pathol Med. 2005;34(5):298–307. doi: 10.1111/j.1600-0714.2004.00300.x
[14] Abel MD, Carrasco LR. Ehlers-Danlos syndrome: classifications, oral manifestations, and dental considerations. Oral Surg, Oral Med Oral Pathol Oral Radiol Endod. 2006;102(5):582–590. doi: 10.1016/j.tripleo.2006.03.018
[15] Fridrich KL, Fridrich HH, Kempf KK, et al. Dental implications in Ehlers-Danlos syndrome. A case report. Oral Surg Oral Med Oral Pathol. 1990;69 (4):431–435. doi: 10.1016/0030-4220(90)90374-2
[16] Mitakides J, Tinkle BT. Oral and mandibular manifestations in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):220–225. doi: 10.1002/ajmg.c.31541
[17] Berglund B, Björck E. Women with Ehlers-Danlos syndrome experience low oral health-related quality of life. J Orofac Pain. 2012;26(4):307–314.
[18] Berglund B, Nordström G, Lützén K. Living a restricted life with Ehlers-Danlos syndrome (EDS). Int J Nurs Stud. 2000;37(2):111–118. doi: 10.1016/S0020-7489(99)00067-X
[19] Mitakides JE. The effect of Ehlers-Danlos syndromes on TMJ function and craniofacial pain. Cranio. 2018;36 (2):71–72. doi: 10.1080/08869634.2018.1435092
[20] Berglund B, Anne-Cathrine M, Randers I. Dignity not fully upheld when seeking health care: experiences expressed by individuals suffering from Ehlers-Danlos syndrome. Disabil Rehabil. 2010;32(1):1–7. doi: 10.3109/09638280903178407
[21] Clark CJ, Knight I. A humanisation approach for the management of joint hypermobility Syndrome/Ehlers-danlos syndrome-hypermobility type (JHS/EDS-HT). Int J Qual Stud Health Well-Being. 2017;12 (1):1371993. doi: 10.1080/17482631.2017.1371993
[22] Ilgunas A, Wänman A, Strömbäck M. 'I was cracking more than everyone else': young adults' daily life experiences of hypermobility and jaw disorders. Eur J Oral Sci. 2020;128(1):74–80. doi: 10.1111/eos.12675
[23] Kroenke K, Spitzer RL, Williams JB, et al. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics. 2009;50(6):613–621. doi: 10.1016/S0033-3182(09)70864-3
[24] Lövgren A, Visscher CM, Häggman-Henrikson B, et al. Validity of three screening questions (3Q/TMD) in

relation to the DC/TMD. J Oral Rehabil. 2016;43 (10):729–736. doi: 10.1111/joor.12428
[25] Tinkle B, Castori M, Berglund B, et al. Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-danlos syndrome type III and Ehlers-Danlos syndrome hypermobility type): clinical description and natural history. Am J Med Genet C Semin Med Genet. 2017;175(1):48–69. doi: 10.1002/ajmg.c.31538
[26] Sacheti A, Szemere J, Bernstein B, et al. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manage. 1997;14(2):88–93. doi: 10.1016/S0885-3924(97)00007-9
[27] Molander P, Novo M, Hållstam A, et al. Ehlers–danlos syndrome and hypermobility syndrome compared with other common chronic pain diagnoses—A study from the Swedish quality registry for pain rehabilitation. J Clin Med. 2020;9(7):2143. doi: 10.3390/jcm9072143
[28] Castori M, Camerota F, Celletti C, et al. Ehlers-Danlos syndrome hypermobility type and the excess of affected females: possible mechanisms and perspectives. Am J Med Genet A. 2010;152(9):2406–2408. doi: 10.1002/ajmg.a.33585
[29] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth. 2013;111(1):52–58. doi: 10.1093/bja/aet127
[30] Martin A. An acquired or heritable connective tissue disorder? A review of hypermobile Ehlers Danlos syndrome. Eur J Med Genet. 2019;62(7):103672. doi: 10.1016/j.ejmg.2019.103672
[31] Castori M. Ehlers-danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. ISRN Dermatol. 2012;2012:751768. doi: 10.5402/2012/751768
[32] Hakim A, De Wandele I, O'Callaghan C, et al. Chronic fatigue in Ehlers-Danlos syndrome-Hypermobile type. Am J Med Genet C Semin Med Genet. 2017;175 (1):175–180. doi: 10.1002/ajmg.c.31542
[33] Engelbert RH, Juul-Kristensen B, Pacey V, et al. The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome. Am J Med Genet C Semin Med Genet. 2017;175(1):158–167. doi: 10.1002/ajmg.c.31545
[34] Scheper M, Rombaut L, de Vries J, et al. The association between muscle strength and activity limitations in patients with the hypermobility type of Ehlers-Danlos syndrome: the impact of proprioception. Disabil Rehabil. 2017;39(14):1391–1397. doi: 10.1080/09638288.2016.1196396
[35] Lundegren N. Oral health and self-perceived oral treatment need of adults in Sweden. Swed Dent J Suppl. 2012;2012(223):10–76.
[36] Hakeberg M, Wide Boman U. Self-reported oral and general health in relation to socioeconomic position. BMC Public Health. 2017;18(1):63. doi: 10.1186/s12889-017-4609-9
[37] Lepperdinger U, Zschocke J, Kapferer-Seebacher I. Oral manifestations of Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2021;187(4):520–6. doi: 10.1002/ajmg.c.31941
[38] Oelerich O, Kleinheinz J, Reissmann DR, et al. Correlation between oral health-related quality of life and objectively measured oral health in people with Ehlers–danlos syndromes. Int J Environ Res Public Health. 2020;17(21):8243. doi: 10.3390/ijerph17218243
[39] Schubart JR, Schaefer E, Janicki P, et al. Resistance to local anesthesia in people with the Ehlers-Danlos Syndromes presenting for dental surgery. J Dent Anesth Pain Med. 2019;19(5):261–70. doi: 10.17245/jdapm.2019.19.5.261
[40] St George G, Morgan A, Meechan J, et al. Injectable local anaesthetic agents for dental anaesthesia. Cochrane Database Syst Rev. 2018;7(7):Cd006487. doi: 10.1002/14651858.CD006487.pub2
[41] Wide U, Hakeberg M. Treatment of dental anxiety and phobia—diagnostic criteria and conceptual Model of behavioural treatment. Dent J (Basel). 2021;9(12):153. doi: 10.3390/dj9120153
[42] Bulbena-Cabré A, Baeza-Velasco C, Rosado-Figuerola S, et al. Updates on the psychological and psychiatric aspects of the Ehlers-Danlos syndromes and hypermobility spectrum disorders. Am J Med Genet C Semin Med Genet. 2021;187(4):482–490. doi: 10.1002/ajmg.c.31955
[43] Cederlöf M, Pettersson E, Sariaslan A, et al. The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. Am J Med Genet B Neuropsychiatr Genet. 2016;171b(2):153–159. doi: 10.1002/ajmg.b.32386
[44] Ishiguro H, Yagasaki H, Horiuchi Y. Ehlers-Danlos Syndrome in the field of psychiatry: a review. Front Psychiatry. 2021;12:803898. doi: 10.3389/fpsyt.2021.803898
[45] Doan L, Manders T, Wang J. Neuroplasticity underlying the comorbidity of pain and depression. Neural Plast. 2015;2015:504691. doi: 10.1155/2015/504691
[46] Li JX. Pain and depression comorbidity: a preclinical perspective. Behav Brain Res. 2015;276:92–8. doi: 10.1016/j.bbr.2014.04.042
[47] Kindgren E, Quiñones PA, Knez R. Prevalence of ADHD and autism spectrum disorder in children with hypermobility spectrum disorders or hypermobile Ehlers-Danlos syndrome: a retrospective study. Neuropsychiatr Dis Treat. 2021;17:379–388. doi: 10.2147/NDT.S290494
[48] Baeza-Velasco C, Cohen D, Hamonet C, et al. Autism, joint hypermobility-related disorders and pain. Front Psychiatry. 2018;9:656. doi: 10.3389/fpsyt.2018.00656
[49] Kapferer-Seebacher I, Schnabl D, Zschocke J, et al. Dental manifestations of Ehlers-Danlos syndromes: a systematic review. Acta Derm Venereol. 2020;100(7): adv00092. doi: 10.2340/00015555-3428
[50] Kaufman CS, Butler MG. Mutation in TNXB gene causes moderate to severe Ehlers-Danlos syndrome. World J Med Genet. 2016;6(2):17–21. doi: 10.5496/wjmg.v6.i2.17
[51] Juul-Kristensen B, Schmedling K, Rombaut L, et al. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. Am J Med Genet C Semin Med Genet. 2017;175(1):116–147. doi: 10.1002/ajmg.c.31540

[52] McGillis L, Mittal N, Santa Mina D, et al. Utilization of the 2017 diagnostic criteria for hEDS by the Toronto GoodHope Ehlers-Danlos syndrome clinic: a retrospective review. Am J Med Genet A. 2020;182 (3):484–492. doi: 10.1002/ajmg.a.61459
[53] Symoens S, Syx D, Malfait F, et al. Comprehensive molecular analysis demonstrates type V collagen mutations in over 90% of patients with classic EDS and allows to refine diagnostic criteria. Hum Mutat. 2012;33(10):1485–93. doi: 10.1002/humu.22137
[54] Hagberg C, Berglund B, Korpe L, et al. Ehlers-Danlos Syndrome (EDS) focusing on oral symptoms: a questionnaire study. Orthod Craniofac Res. 2004;7 (3):178–185. doi: 10.1111/j.1601-6343.2004.00288.x
[55] Di Giacomo P, Celli M, Ierardo G, et al. Evaluation of temporomandibular disorders and comorbidities in patients with Ehler–Danlos: clinical and digital findings. J Int Soc Prev Community Dent. 2018;8 (4):333–338. doi: 10.4103/jispcd.JISPCD_103_18
[56] Diep D, Fau V, Wdowik S, et al. Temporomandibular disorders and Ehlers-Danlos syndrome, hypermobility type: a case-control study. Rev Stomatol Chir Maxillofac Chir Orale. 2016;117(4):228–233. doi: 10.1016/j.revsto.2016.07.009
[57] Bech K, Fogh FM, Lauridsen EF, et al. Temporomandibular disorders, bite force and osseous changes of the temporomandibular joints in patients with hypermobile Ehlers-Danlos syndrome compared to a healthy control group. J Oral Rehabil. 2022;49 (9):872–83. doi: 10.1111/joor.13348
[58] Castori M, Voermans NC. Neurological manifestations of Ehlers-Danlos syndrome(s): A review. Iran J Neurol. 2014;13(4):190–208.
[59] Jerjes W, Upile T, Shah P, et al. TMJ arthroscopy in patients with Ehlers Danlos syndrome: case series. Oral Surg, Oral Med Oral Pathol Oral Radiol Endod. 2010;110(2):e12–20. doi: 10.1016/j.tripleo.2010.03.024
[60] Okeson JP. Management of temporomandibular disorders and occlusion. 7th ed. Mosby, St. Louis, Missouri: Mosby; 2013.
[61] Voermans NC, Knoop H, Bleijenberg G, et al. Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. J Pain Symptom Manage. 2010;40(3):370–8. doi: 10.1016/j.jpainsymman.2009.12.026
[62] Stanitski DF, Nadjarian R, Stanitski CL, et al. Orthopaedic manifestations of Ehlers-Danlos syndrome. Clin Orthop Relat Res. 2000;2000(376):213–221. doi:10.1097/00003086-200007000-00029
[63] Rombaut L, Malfait F, De Wandele I, et al. Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. Arch Phys Med Rehabil. 2011;92(7):1106–12. doi: 10.1016/j.apmr.2011.01.016
[64] Basalom S, Rauch F. Bone disease in patients with Ehlers-Danlos Syndromes. Curr Osteoporos Rep. 2020;18(2):95–102. doi: 10.1007/s11914-020-00568-5
[65] Rombaut L, Malfait F, Cools A, et al. Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil. 2010;32 (16):1339–1345. doi: 10.3109/09638280903514739
[66] Castori M, Morlino S, Ghibellini G, et al. Connective tissue, Ehlers-Danlos syndrome(s), and head and cervical pain. Am J Med Genet C Semin Med Genet. 2015;169c(1):84–96. doi: 10.1002/ajmg.c.31426
[67] Bendik EM, Tinkle BT, Al-Shuik E, et al. Joint hypermobility syndrome: a common clinical disorder associated with migraine in women. Cephalalgia. 2011;31 (5):603–13. doi: 10.1177/0333102410392606
[68] Castori M, Morlino S, Pascolini G, et al. Gastrointestinal and nutritional issues in joint hypermobility syndrome/Ehlers-danlos syndrome, hypermobility type. Am J Med Genet C Semin Med Genet. 2015;169c(1):54–75. doi: 10.1002/ajmg.c.31431
[69] Türp JC, Kowalski CJ, Stohler CS. Temporomandibular disorders–pain outside the head and face is rarely acknowledged in the chief complaint. J Prosthet Dent. 1997;78(6):592–595. doi: 10.1016/S0022-3913(97)70010-6
[70] Macfarlane TV, Blinkhorn AS, Davies RM, et al. Predictors of outcome for orofacial pain in the general population: a four-year follow-up study. J Dent Res. 2004;83(9):712–7. doi: 10.1177/154405910408300911
[71] Yekkalam N, Wänman A. Association between signs of hyperalgesia and reported frequent pain in jaw-face and head. Acta Odontol Scand. 2021;79(3):188–93. doi: 10.1080/00016357.2020.1814963
[72] Di Stefano G, Celletti C, Baron R, et al. Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/Ehlers-danlos syndrome, hypermobility type. Eur J Pain. 2016;20(8):1319–1325. doi: 10.1002/ejp.856
[73] Camerota F, Celletti C, Castori M, et al. Neuropathic pain is a common feature in Ehlers-Danlos syndrome. J Pain Symptom Manage. 2011;41(1):e2–4. 41. United States. doi: 10.1016/j.jpainsymman.2010.09.012
[74] Leone CM, Celletti C, Gaudiano G, et al. Pain due to Ehlers-Danlos syndrome is associated with deficit of the endogenous pain inhibitory control. Pain Med. 2020;21 (9):1929–35. doi: 10.1093/pm/pnaa038
[75] Chopra P, Tinkle B, Hamonet C, et al. Pain management in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):212–219. doi: 10.1002/ajmg.c.31554
[76] Castori M, Morlino S, Celletti C, et al. Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type): principles and proposal for a multidisciplinary approach. Am J Med Genet A. 2012;158a(8):2055–2070. doi: 10.1002/ajmg.a.35483
[77] Bathen T, Hångmann AB, Hoff M, et al. Multidisciplinary treatment of disability in Ehlers-Danlos syndrome hypermobility type/hypermobility syndrome: a pilot study using a combination of physical and cognitive-behavioral therapy on 12 women. Am J Med Genet A. 2013;161a(12):3005–3011. doi: 10.1002/ajmg.a.36060
[78] Nationella riktlinjer för vuxentandvård 2011 [Available from: http://www.socialstyrelsen.se/tandvardsriktlinjer.
[79] Weinberg J, Doering C, McFarland EG. Joint surgery in Ehlers-Danlos patients: results of a survey. Am J Orthop (Belle Mead NJ). 1999;28(7):406–9.

[80] Kühne A, Kleinheinz J, Jackowski J, et al. Study to investigate the knowledge of rare diseases among dentists, orthodontists, Periodontists, oral surgeons and craniomaxillofacial surgeons. Int J Environ Res Public Health. 2020;18(1):139. doi: 10.3390/ijerph18010139

[81] Rombaut L, Deane J, Simmonds J, et al. Knowledge, assessment, and management of adults with joint hypermobility syndrome/Ehlers-danlos syndrome hypermobility type among Flemish physiotherapists. Am J Med Genet C Semin Med Genet. 2015;169c (1):76–83. doi: 10.1002/ajmg.c.31434

[82] Hanisch M, Wiemann S, Bohner L, et al. State of knowledge about information sources and health care centres for rare diseases among affected people in Germany. Cent Eur J Public Health. 2020;28(1):82–4. doi: 10.21101/cejph.a5652

[83] Gray RJ, Davies SJ. Occlusal splints and temporomandibular disorders: why, when, how? Dent Update. 2001;28(4):194–9. doi: 10.12968/denu.2001.28.4.194

[84] Slade GD, Ohrbach R, Greenspan JD, et al. Painful temporomandibular disorder: decade of discovery from OPPERA studies. J Dent Res. 2016;95 (10):1084–92. doi: 10.1177/0022034516653743

[85] Robbins SM, Cossette-Levasseur M, Kikuchi K, et al. Neuromuscular activation differences during gait in patients with Ehlers-Danlos syndrome and healthy adults. Arthritis Care Res (Hoboken). 2020;72 (11):1653–62. doi: 10.1002/acr.24067

[86] Nielsen RH, Couppé C, Jensen JK, et al. Low tendon stiffness and abnormal ultrastructure distinguish classic Ehlers-Danlos syndrome from benign joint hypermobility syndrome in patients. FASEB J. 2014;28 (11):4668–76. doi: 10.1096/fj.14-249656

[87] Rombaut L, Malfait F, De Wandele I, et al. Muscle-tendon tissue properties in the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken). 2012;64(5):766–772. doi: 10.1002/acr.21592

[88] Nygaard RH, Jensen JK, Voermans NC, et al. Skeletal muscle morphology, protein synthesis, and gene expression in Ehlers-Danlos syndrome. J Appl Physiol. 2017;123 (2):482–488. doi: 10.1152/japplphysiol.01044.2016

[89] Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85(3):317–332. doi: 10.1016/S0304-3959(99)00242-0

[90] Hanisch M, Blanck-Lubarsch M, Bohner L, et al. Oral conditions and oral health-related quality of life of people with Ehlers-Danlos syndromes (EDS): a questionnaire-based cross-sectional study. Medicina (Kaunas). 2020;56(9):448. doi: 10.3390/medicina56090448