Chapter 22. Clinical profiling and tailored non-pharmacological treatment in hypermobility spectrum disorders/hypermobile Ehlers-Danlos syndrome

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1. Introduction

In the last decade, scientific research in the area of hypermobility related disorders has grown exponentially. Despite the accumulation of scientific knowledge, these categories of patients remain challenging for most clinicians due to many issues surrounding aetiology, disease classification, diagnostics and treatment. Even for experienced physicians it remains hard to correctly identify patients and to determine which factors should be modified in order to get positive treatment outcomes. Historically, the diagnoses Benign Joint Hypermobility Syndrome (BJHS) and Ehlers Danlos Syndrome; hypermobility type (EDS-HT) were viewed as separate entities, however over the years it became clear that the diagnostic criteria had considerable overlap and were often found to be clinically indistinguishable. With the accumulation of scientific knowledge on both BJHS and EDS-HT, it became apparent that a revision of the diagnostic criteria was necessary in order to improve clinical care and scientific advances. In 2017, the diagnoses BJHS/EDS-HT were replaced by new diagnostic entities in terms of Hypermobility Spectrum Disorders (HSD) and Hypermobile Ehlers-Danlos Syndrome (hEDS; for diagnostic criteria see chapter 2, table 2-5).[1,2] Although scientific research on populations diagnosed according to the new theoretical framework and nosology is limited, the current chapter provides a theoretical framework which will aid clinicians in creating a personalized treatment strategy. The authors recognize that the evidence used within this chapter is based on scientific observations gathered on the old diagnostic criteria and that further research with the new diagnostic criteria is crucial in order to provide the most optimal care. Therefore the current theoretical framework should be viewed as conceptual and only serves as a starting point for clinical care.

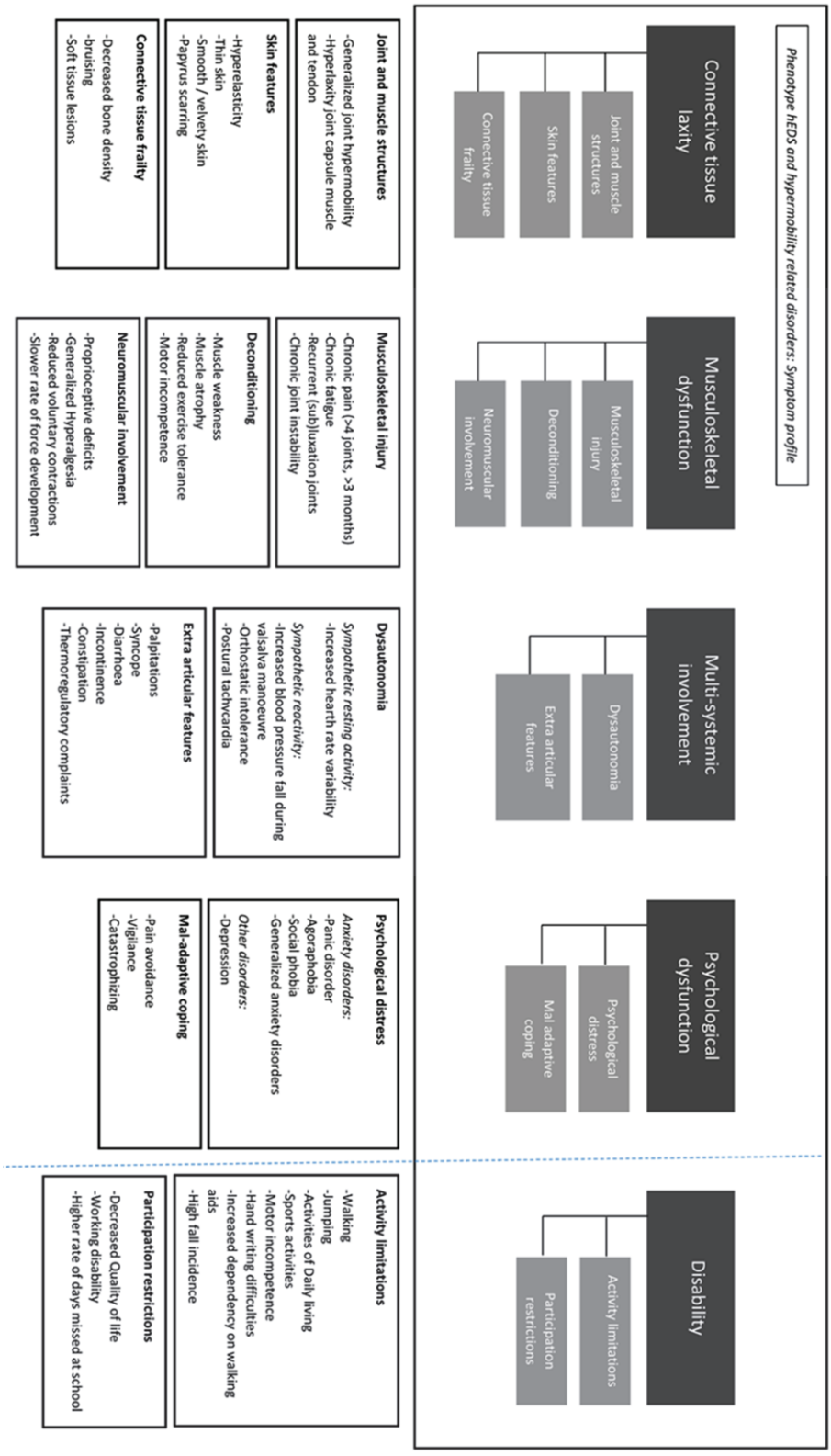
The objective of this chapter is to provide clinicians with a clinical model of hEDS and HSD for which treatment can be optimized to the needs of the individual patient. Due to the complexity of the symptom profiles of HSD/hEDS, the international classification of functioning (ICF) will be adopted as a central framework. The ICF is a multidimensional model of functioning with activities and participation as the key construct. This model provides a framework to describe limitations associated with an individual's functioning and identifies influencing environmental factors. On this framework a clinical profile and treatment strategy can be based.

2. Clinical profiles

2.1 Clinical profiling

Traditionally individuals with BJHS/EDS-HT are characterized by the presence of connective tissue laxity, in terms of Generalised Joint Hypermobility (GJH), hyperextensible skin and arthralgia. However over the years, it became clear that the nature of these disorders is far more complex and can be viewed as a unique pathological entity within the field of rheumatology.[3,4] This is now recognized within the new diagnostic criteria of HSD/hEDS.[1] In order to ensure maximum treatment efficiency, it is essential to have an accurate individual patient's clinical profile that enables the health care provider to target the specific factors that will enhance functional recovery. The clinical profile is based on four clinical components (figure 22-1): (1) Connective tissue laxity, (2) Musculoskeletal dysfunction, (3) Multi-systemic involvement and (4) Psychological dysfunction.

Figure 22-1 Phenotype of hyermobile EDS and hypermobility related disorders: symptom profile



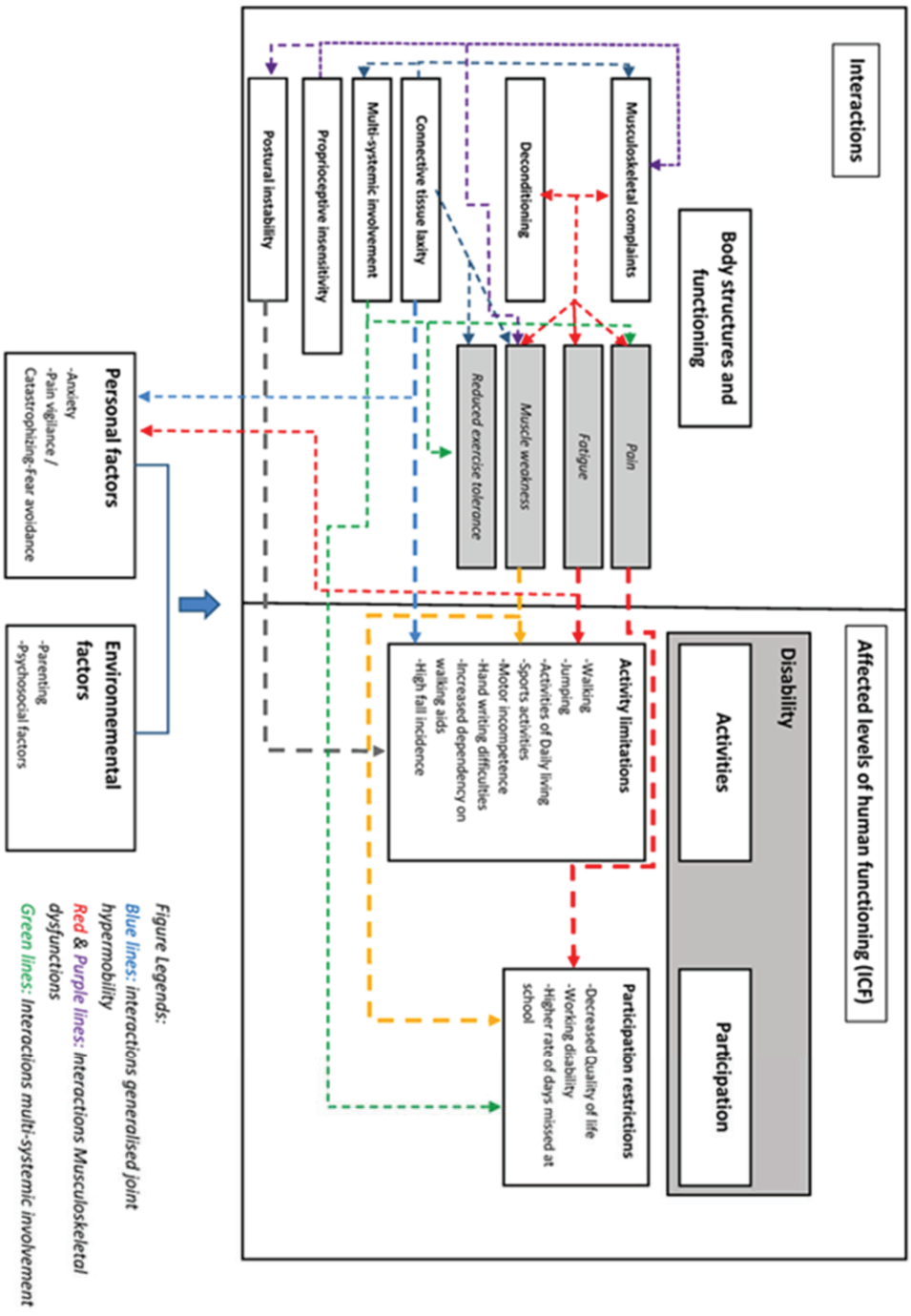
2.1.1 Component 1: Connective tissue laxity

It is assumed that GJH is an expression of generalized connective tissue laxity, in which joint capsules, ligaments, tendons and muscle structures are hyperextensible.[5-7] Therefore, in HSD/hEDS the presence of GJH according to the Beighton criteria is a clinical feature. The Beighton score is considered as the gold standard from infancy to old age, and has been the most used instrument to classify GJH. Originally, the Beighton score was developed for use in research and not designed for clinical use (personal communication of Beighton). Although several studies confirmed good reliability and face validity, a considerable variation in test procedures has been described. This concerns not only the practical instruction of how to perform the various tests, but maybe more importantly, also variations in the cut-off level for a positive test and in the definition of GJH.[3] It remains unclear which cut-off level is the most appropriate. In the previous classifications a score of ≥4 (EDS-HT ≥5) is considered to be the minimum level for GJH, independent of age, gender and ethnicity.[8] Other cut-offs of ≥5, ≥6, ≥7 have also been suggested, but the validity of these cut-off values can be debated. Recent studies have shown that a Beighton score of ≥6 at the age of 10 is a predictor for pain recurrence and persistence at 14 years,[9-11] and a Beighton score of ≥6 at the age of 14 is a predictor for general pain at 18 years of age.[12] This would suggest that scores ≥5 would be more appropriate. However with increasing age, joint laxity decreases, which may imply that a cut-off level of ≥4 eventually may be more appropriate.[13] In addition, gender and ethnicity specific effects on joint laxity have been documented and should also be incorporated in the classification of GJH (see chapter 2 for age and sex related cut-off values for the Beighton score, used in the new criteria of hEDS). The Beighton score requires information on hypermobility in 4 joints (thumb, little finger, elbow and knee) and spine, whereas no information is required on other joints, e.g. shoulder and hip joint. Within the current diagnostic criteria, no such distinction is made. Furthermore, there is little knowledge on the natural course of GJH with increasing age, which also complicates clinical diagnostic procedures.[14,15]

Skin features are the second most distinguishing clinical characteristic that is related to connective tissue laxity. Hyperelasticity, scarring, bruising, smooth and velvety skin have been incorporated into the diagnostic criteria;[16] however the methods of assessment have not been specified in either Villefranche nor Brighton criteria sets (see chapter 2 for criteria for skin hyperextensibility).[3]

Recent research (figure 22-2: blue connections) has shown that the presence and grade of GJH are clinical findings that are directly associated with disability.[17,18] They have also been demonstrated to be associated with pain, fatigue, muscle weakness, dysautonomia and anxiety.[5,17-20]

Figure 22-2 Suspected interactions and relations of symptoms in the context of the International Classification of Functioning, Disability and Health (ICF)



2.1.2 Component 2: Musculoskeletal dysfunction

The presence of chronic pain is a frequent clinical feature that is present in many patients diagnosed with HSD/hEDS and a major diagnostic criteria in the BJHS and EDS-HT diagnoses. Pain is often characterized from mild to severe, affecting multiple joints which may vary over time and may occur episodically but sometimes persists and becomes chronic. In a selected group of patients with musculoskeletal pain seeking specialized care, GJH is prevalent in 9%-57%,[12,18,21,22] exceeding the anticipated prevalence scores of 10-20% in the general population.[23] Although this increased prevalence for GJH in chronic pain patients is striking, a minority of persons with GJH will probably develop a chronic pain syndrome, which negatively impacts daily life, interferes with work and leisure time activities (figure 22-2: red connections).[12,18,21,22] Pain can also directly modify muscle strength and proprioception dependent modalities, which may cause additional deconditioning and loss of motor control through reflex inhibition.[24] The second dominant symptom is fatigue.[25] Fatigue is highly prevalent amongst individuals with GJH[26], HSD/BJHS, and is considered by patients to be one of the most disabling symptoms. Recent literature shows that in 75% of all included patients with EDS-HT/BJHS severe chronic fatigue was present.[25] In patients who were more severely fatigued, higher levels of impairment and psychological distress were present (figure 22-2: red connections).[26]

It is assumed that deconditioning occurs as a consequence of (in)activity related overuse which results in under-activity in order to recover.[27] Consequently, there is a downward spiral of less activity due to fear and more pain with less provocation, leading to deconditioning.[27] Reduced exercise capacity and muscle weakness have been extensively documented in BJHS/EDS-HT patients, and have also been shown in high-level athletes with GJH and healthy individuals with GJH in the absence of chronic pain. The presence of muscle weakness and reduced exercise tolerance in asymptomatic GJH may imply that deconditioning also directly (i.e. not via under-activity) is associated with connective tissue laxity.[17,18,28] Scientific literature shows that muscle weakness is an important clinical finding that is not only associated with disability (figure 22-2: yellow connections), but has also been found to be strongly associated with pain and fatigue (figure 22-2: red connection).

In the last decades, evidence has accumulated on the existence in the symptom profile of BJHS/EDS-HT of a neurological pathway, in which proprioception (peripheral nervous system) and generalized hyperalgesia (central nervous system) are implicated in the development of pain. Proprioception is a specialized sensory modality that provides information about position, movement and sense of resistance which is transmitted by a variety of sensory receptors in the periphery.[30] In theory, proprioceptive deficits may disrupt motor control and cause joint instability which in turn may lead to micro-fractures on joint surfaces. Literature to date only reports the incidence of proprioceptive deficits, with no evidence on the clinical relevance of these findings nor on their role in the development of complaints in subjects with GJH.[18,29]

The presence of generalized hyperalgesia in adult patients with EDS-HT has been described.[30] Subjects with EDS-HT had considerably lower pain pressure thresholds in symptomatic and asymptomatic areas, compared to healthy controls. It was hypothesized that central orientated upregulating processes are present within the central nervous system. Due to centralized sensitization, subjects with BJHS/EDS-HT may be more susceptible to pain and fatigue. Recently these neurological features have also been described in children and were found to be discriminative between BJHS/EDS-HT, GJH and healthy controls.[31]

2.1.3 Component 3: Multi-systemic involvement

Although EDS-HT/BJHS is traditionally viewed as a disease with primary locomotor complaints, in some patients multi-systemic symptoms dominate the symptom profile. Multi-

systemic complaints like gastro-intestinal issues, incontinence as well as dysautonomia have been documented.[4,14,18-21,32,33] Regarding sympathic regulation, patients tend to have abnormalities within both sympathetic resting activity and sympathetic reactivity.[23,24] Dysautonomia manifesting in erratic heart-rate (heart rate variability), as well as reactions on sudden changes of external stimuli, such as blood pressure fall during Valsalva manoeuvre, orthostatic intolerance and postural tachycardia, have also been shown as an integral part of the phenotype of JHS/hEDS.[19,20]

Multi-systemic signs and symptoms have been found to be directly associated with disability in terms of decreased quality of life (figure 22-2: green connections).[19,20] In addition, a positive association with connective tissue laxity, pain and deconditioning has been shown, indicating that with increasing severity of multi-systemic symptoms, the severity of perceived pain and deconditioning increases.[19,20] In children with BJHS/EDS-HT, it has been demonstrated that the presence of multi-systemic features like postural orthostatic tachycardia, skin scarring, bowel issues and chronic diarrhoea were found to be predictive for escalating pain, fatigue, muscle weakness and progressive disability.[34] The importance of multi-systemic features have only been established in children and are not yet established in adults, however it is assumed that multi-systemic features are also an important clinical feature in adults as well.

2.1.4 Component 4: Psychological dysfunction

The impact of BJHS/EDS-HT on daily life seems not to be solely explained by a person's level of hypermobility.[35] High Beighton scores alone do not account for more impairments in daily life. It seems that besides biomedical factors, psychosocial factors also contribute to a person's level of disability. In the chronic pain literature, a fear-avoidance model has been introduced to explain the disabling role of pain-related fear,[36] which has been confirmed by numerous studies.[36-38] It states that highly fearful persons who tend to catastrophize, will avoid activities they perceive as harmful or pain provoking. In the long term, this avoidance behaviour can result in disability, deconditioning and depression, further fuelling the vicious circle of disabling musculoskeletal pain.

It could be that pain related fear will have an accumulating disabling effect in hypermobile persons with pain. In the case of a new onset of musculoskeletal pain, fear of pain will trigger avoidance of painful muscle contractions, leading to subnormal muscle performance. For persons with joint hypermobility, it is hypothesized that subnormal muscle performance will possibly have the immediate negative consequence that the muscles' compensation mechanism, essential for joint stability, will fail. Functional consequences, such as impaired balance ability and reduced balance confidence, will further fuel fear of movement and catastrophizing thoughts about pain and vice versa. In fearful hypermobile patients, a painful stimulus can thus, even in the short term, lead to a high level of disability, depression and disuse.[39]

The high prevalence of both anxiety and joint hypermobility in patients with musculoskeletal pain, could indicate that this hypothesized mechanism may explain disability in a substantial subgroup of patients.[35] A finding that seems to support a common pathway for hypermobility and anxiety, is an increased prevalence score for joint hypermobility in patient populations with other anxiety related problems: 62% of patients with a panic disorder appeared to be hypermobile.[40]

2.2 Clinical profile assessment

When considering the highly heterogeneous clinical presentation of EDS-HT/BJHS or HSD/hEDS patients, simply classifying each individual on the basis of criteria will not suffice and may even lead to an unsuccessful treatment.[18,21,32] Therefore, it is essential that each

patient is profiled on all aspects of the ICF model to enable the creation of an individualized tailored treatment regime.[41] Currently no international consensus exists on which outcomes are the most clinically relevant and by which measures these should be assessed.[6,14,18,21,27,32] The recommendations presented in this paragraph for the clinical profile assessment should be merely viewed as recommendations and should be adjusted to the individual context of each health professional (e.g. available equipment, time constraints, training) and patient (e.g. cognitive level, physical issues that render the patient unfit to be tested). The suggested clinical profile will consist of the previously mentioned components: disability, connective tissue laxity, musculoskeletal dysfunction, multi-systemic involvement and psychological dysfunction. It should be pointed out that when engaging in a diagnostic assessment of a HSD/hEDS patient, multi-disciplinary cooperation is vital and may even be considered as a necessity. The presented examples of outcome measures are derived from literature and personal experience of the authors.

2.2.1 Disability

Disability is a multi-dimensional concept defined as a patient-oriented health outcome which contains aspects of individual daily functioning, including physical, psychological and social factors.[42] Reducing disability is often used as a primary outcome in a variety of study designs, whereas an operational definition is frequently lacking.[43] It can, however, be operationalized in both capacity and performance measures, where capacity refers to what a patient can do in a standardized environment, and performance to what a person does in daily life.[44,45] Regarding capacity qualifiers, it can be advised that standardized tests on functional outcomes like walking, transfers and activities of daily living are incorporated. A functional assessment based on the specific needs of the patient would form an integral part of the assessment which should be complemented by standardized testing. Standardized tests like the 6 minute walk test,[46,47] and chair rise test[47] would be suitable and are frequently used in clinical practice. In addition, for these measures there are normal values available as an aid in the assessment of the grade of disability. Currently, more modern measures of disability are available in terms of continuous activity monitoring. Although these measures are more costly and not often used in clinical practice, it could be recommended that when a more detailed assessment of activity patterns is indicated, these type of outcome measures are applied, especially in children.[48] Measures of disability performance are often assessed during medical history taking and should be complimented by questionnaires. Assessors should choose the most appropriate set of questionnaires, based on age, goal and patient preference. Generic questionnaires like the Health Assessment Questionnaire[49] and the Child Health Assessment Questionnaire[50] are recommended as they have been validated, have normal values, account for the use of assistive devices, and are available in multiple languages.

2.2.2 Connective tissue laxity

It is recommended that connective tissue laxity is assessed when joints and skin are relaxed, by observation and testing. A general view on the grade of laxity may be informative on the status of connective tissue; however no evidence is available that shows that disease severity is associated with increasing connective tissue laxity.[5] The presence of GJH according to the Beighton score is traditionally scored within the diagnostic criteria, but should also be monitored over time. When using the Beighton score it is crucial that it is performed according to a standardized protocol and more importantly, assessors should be well experienced when using the Beighton score.[8] Despite the simple appearance of the Beighton score and its applicability, it should not be underestimated and intensive training / inter-assessor consensus is essential.[8] The protocol by Smits et al., which makes use of a goniometer in order to increase precision, can be recommended for the standardisation of the

Beighton score.[51] GJH is classified if a score of ≥5 is obtained, when using the Villefranche criteria, irrespective of age, gender and ethnicity. Despite the central role of GJH in the diagnostic criteria, much discussion exists on the cut-off value for GJH.[3] Therefore, it is recommended that other measures of joint mobility are incorporated in the assessment of connective tissue laxity like goniometry and skin laxity. Goniometry with proper training can be a valuable tool for assessing individual joints,[52] especially when comparing measurements with normal values. Skin assessment should be performed by visual inspection on the appearance of the skin (bruising, scarring) and palpation (smooth, velvety feel). A general inspection of the whole body is recommended. Regarding skin laxity, manual testing at the volar aspect of the forearm is frequently applied and is sufficient in order to identify hyperextensibility (yes/no). More advanced measures of skin extensibility are available; however, their clinical relevance has not yet been established.

2.2.3 Musculoskeletal dysfunction

Regarding pain, it is important to not only document its location but also its severity and duration. Traditional measures like the visual analogue scale (VAS) or numeric rating scale (NRS) are often included in the clinical assessment. It is important to quantify pain as a general measure but also to assess the pain intensity for each individual location.[53] Pain body schemes like the Pain Manakin not only provide information on the location of pain but can also be converted into a percentage of painful body surface, which informs on the spread of pain.[54] Also pain sensitivity measurement may be a useful addition to the clinical profile, by assessing pain pressure thresholds, which inform on the sensitivity for pain.[30] Fatigue can be assessed in a similar way as pain severity by VAS or NRS; however, chronic fatigue may also be viewed as a state in which biological fatigue is hard to discriminate from mental fatigue. Questionnaires like the Checklist Individual Strength[26] in adults and the Multi-dimensional Fatigue Scale in children[55] are examples of questionnaires which assess the full scope of fatigue related problems.

Muscle weakness can be assessed by the use of handheld dynamometers,[56] which can accurately quantify the extent of muscle force and can be related to age and gender related normal values. However, these measures do not necessary represent functional muscle strength. Therefore, it is recommended that functional strength measures are incorporated, such as repeated functional tasks (e.g. squatting, lifting), sit to stand, walking stairs, one leg stand, and jump tests (single leg hop, sidehop test).[18,45] Manual muscle strength tests are not advised as they are only informative on muscle strength symmetry and are not suited to quantify and compare muscle force between patients.[56] Cardiovascular exercise tolerance testing may also be indicated.[57] Both bike (e.g. steep ramp protocol) and walk tests (e.g. Bruce treadmill exercise test) can be applied, depending on the available equipment. However, when engaging in maximal exercise testing, safety issues should be addressed and constant monitoring should be applied as a risk of cardiac complications is present. Field based tests like the shuttle walk test or stair climb test may serve as less intensive measures that can also estimate exercise capacity.[58] Muscle weakness may also be caused by other medical conditions, e.g. neurological diseases; therefore differential diagnostics remains important.

Proprioceptive deficits are mentioned frequently in medical literature and are often implicated as a potential cause for the development of pain. However, measures of proprioception are quite sophisticated and often not applicable in clinical practice. Standing balance (e.g. Romberg test, stork test) or functional observations on motor control/clumsiness may be more feasible.[59]

2.2.4 Multi-systemic involvement

Multi-systemic involvement can present itself in numerous ways and is often missed by clinicians. Medical history assessment should involve specific questions regarding gastro-intestinal complaints (organ dysfunction: abdominal pains, diarrhoea, constipation, incontinence), fainting (dysautonomia: syncope and presyncope), perceived heart beat irregularities (dysautonomia: palpitations) and issues of thermo-regulation after exercise (dysautonomia: like elevated body temperature). As the spectrum of these types of signs and symptoms is quite broad, the use of a standardized questionnaire is advised. Examples of such questionnaires are the Autonomic Symptom Profile[20] and the Somatic Complaint List.[60] Measures specifically focused on dysautonomia, like the tilt test, are not advised as they involve specialized protocols and strict medical supervision.

2.2.5 Psychological dysfunction

Psychological dysfunction should be screened for in every patient and may prove to be invaluable during the treatment process. If psychological dysfunction is present, the expertise of a psychologist is indicated and should be incorporated in the treatment procedures. Screening for this dysfunction can be viewed as essential and needs to be performed on each patient. As time and disease symptoms progress, the odds of developing psychological dysfunction increase. At medical history assessment, clinicians should be aware of potential signs of depression (fatigue, mood, loss of initiative and appetite), anxiety and pain avoidance (anxiety associated with specific activities and or pain). Questionnaires for adults like the Hospital Anxiety and Depression Scale (HADS), a short questionnaire,[18] and the Symptom Checklist (SCL-90),[61] a more extensive questionnaire are useful generic measures of psychological dysfunction and are recommended. In children, the Revised Child Anxiety and Depression Scale, a short questionnaire,[62] or the Child Behaviour Checklist,[63] a more extensive questionnaire, are recommended.

3. Tailored intervention

Based on the clinical symptom profile, a tailored intervention may be constructed. Recently a consensus was reached by the Ehlers-Danlos Consortium on the rationality of treatment for HSD/hEDS patients. The current paragraph is based on this consensus statement, however it should be viewed as a summary. For a more detailed description of the available evidence for treatment as well as the background of the rationality for treatment we would like to refer to Engelbert et al 2017.[39] The presented recommendations are based on current knowledge available and personal experience and should be adapted to the nature of the clinical profile, patient preference and context. An overview of all included studies on children[18,64,65] and adults[12,66-70] is shown in table 22-1. The best treatment strategy for highly disabled people with hypermobility is likely to be multidisciplinary. In this way, both physical (hypermobility and related deconditioning) and psychosocial (fear, depression, inadequate coping) components associated with pain can be addressed. During this treatment, patients will be guided in how to develop pain management skills and to change unhelpful coping strategies into helpful ones, in order to decrease disability. Based on systematic evaluation, positive effects of multidisciplinary behavioural treatment for patients with chronic pain syndromes have been confirmed.[71] Whether multidisciplinary treatment specifically targeting pain/disability-related problems in hypermobile people is effective or whether it needs further adaptation to this specific group is currently unclear. As Keer and Simmonds mentioned in their review concerning joint protection and rehabilitation in the adult with a hypermobility syndrome,[72] it is not yet known which form the optimal physical rehabilitation programme should adopt. As long as scientific data on optimal treatment is lacking, recommendations can only be made based on ‘best opinion’ (practice-based).[72,73]

In general, all treatment modalities that aim at enhancing physical fitness, in terms of muscle strength and exercise tolerance, have beneficial effects on pain.[12,18] It is crucial when applying a physical training programme that a physiological baseline is established, which will prevent the occurrence of over or undertraining. Due to the unstable nature of the condition, training intensity should be adjusted to physical and psychological changes over time. It should be noted that the retention time of the accomplished treatment effects is limited. Therefore, maintaining adequate physical activity patterns is vital and should be recognised as a priority. The addition of cognitive therapy can also aid in preserving the achieved treatment effects and functional recovery. Although current research indicates that physical training in combination with a cognitive intervention is effective in pain management, effects on disability have not been shown. The addition of proprioceptive and postural control exercises (closed chain) have also been demonstrated as being effective on pain in children and adults. This combination of exercises will not only have effects on muscle power, but also on motor control.[12,65,69]

In recent years it has become clear that treatment intensity is very important. Exercise should be treated just as medicine, in which side effects may occur and the doses should be graded. In the initial phase (clinical profiling) relevant treatment variables are identified; individual goal setting should be the main focus. In the second phase physical training in combination with cognitive interventions (patient education or individualized psychological intervention) should be initiated in a graded fashion. Initially, the primary focus should be on the cognitive aspects and later on, it should be more on the physical aspects with increasing exposure to higher training intensity. During the whole treatment period, cognitive intervention should be part of the treatment regime (depending on the patient profile and his or her progression). In the final phase the focus should be more on education as well as on continuing adequate physical activity with adequate responses to recurrence of injury. In this phase, frequency and duration of patient-therapist contacts should be reduced and the patient should be enabled to be more independent and in control of his/her condition. After treatment has ended, patients are able to manage re-injury and are advised to contact the multidisciplinary treatment team only if required. Assistive devices are often prescribed in order to reduce disability and pain, however the use of such interventions is also controversial. Currently no evidence is available on the effectiveness of supportive devices and walking aids for this category of patients.[39] As conserving and expanding the habitual activity should be a top priority in any intervention for HSD/hEDS[18,34,74], the usage may be beneficial in certain cases however it may also cause further deconditioning and subsequent disability. Therefore, in line with the evidence statement, judicious use of assistive devices and walking aids is advised and should be made on an individual bases.[39]

4. Areas of uncertainty

As mentioned previously, the evidence presented in this chapter is based on patients diagnosed with BJHS/EDS-HT and it remains unclear if these findings are also applicable to patients diagnosed according to the newly adopted diagnostic criteria (HSD/hEDS). Although the new criteria are more specific, which would cause a shift in patient characteristics, it is expected that the basic principles as described in this chapter and in the evidence statement are similar. Recent knowledge on the natural course of disability is now available, in which the importance of multi-systemic issues have been demonstrated, still the pathological mechanisms underlying HSD/hEDS remain obscure.

Future scientific exploration should focus more on longitudinal study designs in order to create (predictive) clinical models of HSD/hEDS from which risk profiles can be derived, with which patient trajectories and multidisciplinary treatment can be optimized. Until that time, clinicians should treat the recommendations in this chapter as guiding principles, which

should be constantly adjusted to the individual patient and his/her environment as well as to the individual context of the healthcare provider.

5. Summary

The diversity in signs and symptoms and the large heterogeneity of clinical presentation among patients with HSD/hEDS often pose a complex problem for healthcare providers in terms of diagnosis, assessment and treatment. The clinical presentation of the phenotype of HSD/hEDS can be described by four components: 1) Connective tissue laxity, 2) Musculoskeletal dysfunction, 3) Multi-systemic involvement, and 4) Psychological dysfunction. On the basis of these components a clinical profile can be derived from which a tailored intervention may be constructed. Although it remains unclear which treatment modalities (or combinations thereof) are best suited for HSD/hEDS, treatment should be tailored to the clinical profile of the patient and be applied in a graded fashion in order to ensure maximum effectiveness.

Addendum by the editors

In the March 2017 issue of the American Journal of Medical Genetics Part C Seminars in Medical Genetics all papers were devoted to EDS, covering a new EDS nosology, new diagnostic criteria of the different types and also management related topics (see also chapter 2). One of these papers is entitled “The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers-Danlos syndrome”.[39]

Table 22-1 Scientific literature regarding treatment modalities of BJHS/EDS-HT

Author (year), individuals	Type of intervention	Brief description of treatment modality	Treatment specifics	Evaluation points	Author conclusion
Bathen et al [68] *(2013)* **Adults**	Physical and cognitive rehabilitation	Multi-disciplinary treatment: Medical, physical/occupational therapy, social worker Clinical admission: combination of physical treatment aiming at enhancing physical fitness (68% of all sessions, n=17), and cognitive intervention on pain management and lifestyle (42% of all sessions, N=8) Home exercise: physical exercise and monitoring by telephone	Total duration: 13.5 weeks Clinical admission:2.5 weeks Home exercise: 12 weeks Frequency: 4 sessions a week Intensity: (?)	Baseline at start of treatment; Re-admission and assessment at 13 weeks (end of treatment)	-Significant changes in perceived performance of daily activities and participation -Significant reduction of kinesiophobia. -Smaller changes in self-perceived pain.
Rahman et al [70] *(2014)* **Adults**	Cognitive oriented approach	Multi-disciplinary: Medical, psychology, physical therapy Cognitive intervention on illness beliefs, pain management, relaxation and lifestyle advice	Total duration: 6 weeks Frequency: 1 to 2 sessions a week Intensity: 7 hours a week	Baseline at start of treatment; 10 weeks after baseline (T1: end of treatment) Follow-up: at 26 weeks after baseline	-Significantly decreased disability and pain at T1. -at follow-up, the gain in disability regressed to baseline level, but the changes in pain perception were retained
Ferrell et al [69] *(2004)* **Adults**	Physical rehabilitation	Mono-disciplinary: physical therapy Home based physical exercise (open and closed chain exercises), aimed at enhancing proprioception, muscle strength and balance.	Total duration: 8 weeks Frequency: 2 times a week Intensity: increasing number of sets and repetitions.	Baseline at start of treatment; End of treatment at 8 weeks	-Disability was significantly decreased after 8 weeks of treatment -Improvements in pain intensity: lower scores on VAS at 8 weeks

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Sahin et al [71] *(2008)* **Adults**	Physical rehabilitation	Mono-disciplinary: physical therapy Clinic based proprioceptive and balance exercises	Total duration: 8 weeks Frequency: 3 times a week Intensity: (?)	Baseline at start of treatment; End of treatment at 8 weeks	-Significantly decreased disability at 8 weeks -Improvements in pain intensity: lower scores on VAS at 8 weeks
Barton et al [67] *(1996)* **Adults**	Physical rehabilitation	Mono-disciplinary: physical therapy Clinic based joint stabilizing exercises	Total duration: 6 weeks Frequency: 3 times a week Intensity: repetitions tailored to individual capabilities. No criteria specified	Baseline at start of treatment; At 6 weeks after baseline (end of treatment) At 12 weeks after baseline (Follow-up)	-Significant improvements in disability and pain at both time points
Pacey et al [65] *(2013)* **Children**	Physical rehabilitation	Mono-disciplinary: physical therapy Clinic based joint stabilizing exercises performed within hypermobile range versus neutral range	Total duration: 8 weeks Frequency: weekly sessions Intensity: 30-60 minutes	Baseline at start of treatment; At 8 weeks after baseline end of treatment); At 12 weeks after baseline (Follow-up)	-Significant improvements in disability and pain at both time points in both groups
Kemp et al [66] (2009) **Children**	Physical rehabilitation	Mono-disciplinary Clinic based proprioceptive and balance exercises versus physical training alone	Total duration: 6 weeks Frequency: once a week Intensity: physical training: 30 seconds intervals. Proprioceptive exercises: No criteria specified	Baseline at start of treatment; At 6 weeks after baseline (midterm of treatment); At 12 weeks after baseline (end of treatment)	Both interventions demonstrated significant pain reduction, but no between- groups difference.

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