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International Perspectives on Joint Hypermobility

A Synthesis of Current Science to Guide Clinical and Research Directions

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Abstract: There is exponential clinical and research interest in joint hypermobility due to recognition of the complexity of identification, assessment, and its appropriate referral pathways, ultimately impacting management. This state-of-the-science review provides an international, multidisciplinary perspective on the presentation, etiology, and assessment of joint hypermobility, as it presents in those with and without a systemic condition. We synthesize the literature, propose standardizing the use of terminology and outcome measures, and suggest potential management directions. The major topics covered are (i) historical perspectives; (ii) current definitions of hypermobility, laxity, and instability; (iii) inheritance and acquisition of hypermobility; (iv) traditional and novel assessments; (v) strengths and limitations of current assessment tools; (vi) age, sex, and racial considerations; (vii) phenotypic presentations; (viii) generalized hypermobility spectrum disorder and hypermobility Ehlers-Danlos syndrome; and (ix) clinical implications and research directions. A thorough understanding of these topics will equip the reader seeking to manage individuals presenting with joint hypermobility, while mindful of its etiology. Management of generalized joint hypermobility in the context of a complex, multisystem condition will differ from that of acquired hypermobility commonly seen in performing artists, specific athletic populations, posttrauma, and so on. In addition, people with symptomatic hypermobility present predominantly with musculoskeletal symptoms and sometimes systemic symptoms including fatigue, orthostatic intolerance, and gastrointestinal or genitourinary issues. Some also display skeletal deformities, tissue and skin fragility, and structural vascular or cardiac differences, and these warrant further medical follow-up. This comprehensive review on the full spectrum of joint hypermobility will assist clinicians, coaches/sports trainers, educators, and/or researchers in this area.

Key Words: Ehlers-Danlos syndromes, heritable disorders of connective tissue, hypermobility spectrum disorder, joint hypermobility, joint laxity

(*J Clin Rheumatol* 2022;00: 00–00)

This article reviews various aspects pertaining to joint hypermobility. These include a historical perspective; current definitions; etiology; traditional and novel assessments and their utility; age, sex, and racial considerations; and phenotypic presentations. The primary aim is to provide a clinical overview about identification of hypermobility forms. The secondary aims are to highlight best available contemporary research on referral pathways and implications for clinical practice to highlight directions for future research. The resulting synthesis of the science article has been contributed to and reviewed by an internationally recognized multidisciplinary team of allied health professionals and medical specialists from the Ehlers-Danlos Syndrome International Consortium, who are tasked to develop evidence-informed management and care guidelines.

HISTORICAL PERSPECTIVES OF JOINT HYPERMOBILITY

Joint hypermobility was recognized as a clinical entity by Hippocrates in the fourth century BC when describing the use of medical interventions to improve capacity for javelin throwing or shooting arrows for family groups experiencing shoulder instability.[1] The literature records similar descriptions from contortionists to musicians.[2] Early reports of excessive joint mobility led to collections of signs and symptoms being ascribed diagnoses in the scientific literature of the late 1800s and early 1900s. In the 1960s, hypermobility syndrome was defined as "the occurrence of symptoms in otherwise healthy hypermobile individuals."[3] The term *Ehlers-Danlos syndromes* was ascribed in the genetic and dermatology fields,[4] whereas the term *joint hypermobility syndrome* (JHS) was used in the rheumatology field.[5] Specialists from these fields recognized the overlap of these conditions more recently,[6] resulting in agreed terminology attributed to specific diagnoses of generalized hypermobility spectrum disorder (G-HSD) and hypermobile Ehlers-Danlos syndrome (hEDS).[7]

CURRENT DEFINITIONS OF HYPERMOBILITY, LAXITY, AND INSTABILITY

Although used interchangeably, the terms *joint hypermobility*, *laxity*, and *instability* are not synonymous. This is not a new phenomenon. In 1902, when reporting on a child with congenital hip dislocation, Ochsner[8] described "hypermobility of the heads of the femora and of the thighs." It is likely that he was referring to physiological motion of the hips (hypermobility) and accessory motion of the femoral heads (laxity).

Hypermobility describes an objective measure of a joint moving passively or actively beyond normal physiological limits

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Open access funding of this article is supported by the EDS International Consortium.

The authors declare no conflict of interest.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.jclinrheum.com).

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ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000001864

around axes of motion.[7] An example is hyperextension or recurvatum of the knee. The proposed multidimensional causes of joint hypermobility include bone morphology/shape seen in humeral and femoral torsion,[9] increased surface area for articulation,[10] and dysplastic or excessively compliant passive restraints to physiological joint motion.[11]

Laxity describes an objective measure of a joint to move passively beyond normal limits during accessory motion (commonly glide and spin).[12] It is assessed using manual tests such as the Lachman test of the knee, anterior drawer of the ankle, or shoulder, or mechanically (e.g., KT-3000, a mechanical device that measures tibial displacement for an imposed load).[13] The terms *laxity* and *mechanical instability* are often used interchangeably.

Functional Instability is a subjective/self-report by the patient as mistrust or insecurity that their joint will remain intact even under low force conditions. They might describe the joint subluxing, going out of place, giving way, or frankly dislocating. Measurement of functional instability or confidence in the joint of interest can be assessed by questionnaire.[14]

In the absence of functional instability (a symptom except where dislocation is evident), any signs of hypermobility and laxity may be clinically irrelevant and may even be an asset. Consider the gymnast who displays extreme physiological joint range of motion (hypermobility) and, if formally assessed, displays accessory motion in excess of what might be expected for his/her age and sex (laxity). Despite hypermobility and laxity, they do not report that their joints subluxate or dislocate during gymnastic routines or activities of daily life. That is, their joints are not unstable and do not need to be "managed" or medicalized. When joints are adequately stabilized by the active system (muscles and tendons) in the presence of adequate proprioception and kinesthesis, such that physiological and accessory motion is controlled, inadequacy of the passive stabilizers (fascia, ligaments, and joint capsules) is disguised. Affected joints become symptomatic (unstable) when the active system fails, which sometimes occurs following injury or deconditioning.

INHERITANCE AND ACQUISITION OF JOINT HYPERMOBILITY

The presentation and distribution of joint hypermobility vary widely between individuals. It may be present as monoarticular (found in a single joint), pauciarticular, or oligoarticular (a few joints), polyarticular (several joints often either central or peripheral, upper or lower limbs), or generalized joint hypermobility (GJH), present in all 4 limbs and the axial skeleton. These forms of hypermobility may be inherited as a normal trait with no identifiable genetic variant or as part of a heritable syndrome such as the Ehlers-Danlos syndromes (EDSs) and other heritable disorders of connective tissue. Joint hypermobility may also be acquired from trauma, joint disease, or training. For example, shoulder range has been shown to be greater in the dominant than nondominant arm of a baseball player.[15] Joint hypermobility may also present bilaterally, for example, in both knees where extension range is reported to increase with training.[16] There are also subpopulations for whom joint hypermobility is an asset such as dancers, musicians, gymnasts, and contortionists, and it is expected that these will have higher prevalence of GJH than the general population.[2,17]

The underlying determinants of GJH remain unknown. Given the trait of GJH running in families, it has been traditionally considered to be an autosomal dominant trait,[18] most likely related to genes encoding collagen or a collagen-modifying enzyme.[19] Candidate genes involved with GJH are, however, broader with joint hypermobility sometimes presenting as one sign of a heritable disorder of connective tissue. For example, one study reported that 5% to 10% of adults with hypermobile EDS demonstrate reduced tenascin-X serum levels.[20] This has broadened the field of candidate genes responsible, as tenascin-X is a large extracellular matrix glycoprotein, the first noncollagenous protein identified with GJH in these conditions.[19] Fragility of connective tissue, the most abundant tissue in the body, may be evident in tendons, septa, fascia, ligaments, and joint capsules due to deficient structural proteins including collagen, elastin, fibrillin, and tenascin.[21] People with heritable disorders of connective tissue with known genetic causes, such as osteogenesis imperfecta,[22] and neuromuscular conditions[23] commonly present with GJH.

A more nuanced understanding of the spectrum of GJH and other copresenting signs, symptoms, and conditions is required. The complex interplay between an individual's genetic and functional physiological interactions and environmental influences contributes to their phenotypic presentation.[24]

TRADITIONAL AND NOVEL ASSESSMENTS OF JOINT HYPERMOBILITY

Interest in the clinical measurement of joint hypermobility has grown since the 1960s when Carter and Wilkinson[25] published an assessment tool. Others from around the world adapted this assessment tool to include other joints relevant to the population of interest. The Nicholas Scale modified this tool to screen football players,[26] and the Rotes-Querol Scale considered additional tests for shoulder, cervical, and lumbar spine mobility.[27] Further development saw the Contompasis Score include a more complex grading system of mobility incorporating the ankle,[28] whereas the Hospital del Mar Scale incorporated knee and shoulder rotation.[29] Modified from the Carter and Wilkinson tool and originally designed to screen for GJH using a single cutoff score, the Beighton score is the most widely used tool[30] (Supplemental Table, http://links.lww.com/RHU/A464). Recent research has demonstrated that extents of hypermobility vary and so recommends variable cutoffs for the age, sex, and cohort of interest based on race, occupation, and so on.[31,32]

More comprehensive peripheral joint hypermobility tools have been developed to provide greater detail and targeted management direction. The Upper Limb Hypermobility Assessment Tool (ULHAT)[33] and Lower Limb Assessment Score[34,35] are both 12-item tests covering the major joints of the upper and lower limbs, in multiple planes of movement (Supplemental Table, http://links.lww.com/RHU/A464). It should be noted that these tools incorporate a few tests of laxity also (described as passive accessory tests in Supplemental Table, http://links.lww.com/RHU/A464).

There are a few points to consider when using hypermobility assessments. Whereas age- and sex-specific cutoff scores have been determined for the Beighton score (Supplemental Table, http://links.lww.com/RHU/A464), these have not been established for the other tools, nor has any psychometric testing been undertaken to elucidate the key items to determine limb hypermobility. Despite a high interlimb mobility correlation,[33–35] there are reports of the nondominant limb being more hypermobile than the dominant[36,37] and side-to-side differences due to training effects.[38]

The 5-part questionnaire is a valid and reliable self-report questionnaire tool that can be used to measure GJH in adults. The tool is particularly useful in adults who have experienced age- and injury-related joint range reduction[39] (Supplemental Table, http://links.lww.com/RHU/A464).

STRENGTHS AND LIMITATIONS OF CURRENT JOINT HYPERMOBILITY ASSESSMENT TOOLS

There are a number of tools designed to assess joint range of movement for which reliability has been evaluated.[33–35,40] It

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should be noted that the Beighton score was designed for epidemiological screening purposes not for clinical use.[30] An advantage of the Beighton score is that it is quick to perform and requires a goniometer only when joint range is equivocal. Limitations include that it is heavily upper-limb biased and that it incorporates a limited number of joints and assesses motion in only 1 plane of movement (sagittal). Perhaps its most significant limitation is that it does not include the joints that patients most commonly describe as unstable such as the shoulder, foot/ankle, and patellofemoral joints.[41,42] While the 5-part Hypermobility Questionnaire has very good sensitivity and specificity for identifying GJH, it has been validated only in adults and does not provide clinicians with information about individual joints. The more recently developed and validated Lower Limb Assessment Score[34,35] and the ULHAT[33] have the potential to provide clinicians with richer insight into joint range and integrity to inform further functional assessments and interventions. These multidimensional assessments, however, require standardized procedures, skilled handling, and further psychometric testing. These insights into assessment strengths and limitations should prompt clinicians to apply the most appropriate assessment tool suited to the patient's presenting signs and symptoms.

AGE, SEX, AND RACIAL CONSIDERATIONS

Epidemiological studies report a large variation in hypermobility prevalence, depending on the clinical assessment method, cutoff score used, population, physical fitness, age, sex, and race.[43] The prevalence of joint hypermobility has been reported as ranging from 5% to 40% in children and 10% to 20% in adults.[44,45] Regardless, the prefix "hyper" signifies that the measure is not "normal," where normal represents the mean and scores within 2 SDs for a population,[46,47] factoring in age, sex, and race.

There is significant complexity in the assessment of joint range of motion of infants and children. Infant joint range of motion is dependent on a newborn's gestational age and is challenging to accurately assess because of a lack of bony landmarks and difficulty determining accurate planes of motion.[48] Beyond the early years, children typically present with greater joint mobility than adults. No current assessments of GJH have been validated in children younger than 5 years and as such cannot be used to accurately identify GJH in this age range. Where available, age-, gender-, and race-specific norms of individual joints[49] can be used to determine hypermobility of a child's individual joints only. Children exhibiting increased joint mobility in multiple individual joints can then be identified. Ongoing monitoring of joint range in children with suspected GJH and any potentially associated symptoms or concerns is recommended throughout the pediatric years before labeling a child with nongenetically confirmed conditions that can be associated with GJH. Although it is well-described that the prevalence of GJH reduces with age it remains unclear which children will continue to demonstrate GJH and which children will "tighten up postpuberty."

Joint hypermobility is more prevalent in females than in males. Although similar age-related trends of joint hypermobility have been reported between sexes, the decrease in joint mobility after puberty is usually more pronounced among males.[45,50] Proposed explanations for these sex-related differences include, but are not limited to, hormonal, anatomical, and neuromuscular differences.[51,52]

Concerning the racial variation of joint hypermobility, several studies suggest a higher prevalence in people of African, Asian, and Middle Eastern descent compared with White populations.[44] Unfortunately, most studies of joint hypermobility do not report on the race of participants. Those that do incept mostly White participants. Consequently, subanalyses to determine the effect of race on joint hypermobility and related signs and symptoms are not possible.

PHENOTYPIC PRESENTATIONS OF JOINT HYPERMOBILITY

Most individuals with hypermobile joints remain asymptomatic throughout their life.[7,53] This hypermobility is labeled as "asymptomatic joint hypermobility" if present in otherwise healthy individuals without any associated symptoms or complications. When the hypermobility is polyarticular or generalized, these individuals often describe themselves as "double jointed" and may undertake pursuits for which joint hypermobility is an asset, such as dancing, music, gymnastics, and contortion (Fig. 1, iceberg on the left).

The symptomatic threshold may be reached when multiple risk factors for pain onset are present in, or in proximity to, a hypermobile joint.[54,55] These factors include muscle weakness,[56] reduced mobility, insufficient musculotendinous length, muscle hypertonicity in proximity to a hypermobile joint, obesity,[57] and altered movement patterns.[42] If hypermobility is present in combination with pain, recurrent (sub)luxations, and musculoskeletal overload injuries,[58] it can be categorized as "symptomatic joint hypermobility" (Fig. 1, left side of symptomatic hypermobility iceberg). A decrease in functional capacity,[59] lower isometric strength,[56] suboptimal muscle activation strategy, and quality of force control[60] have been reported in people with symptomatic joint hypermobility. Despite growing attention in the past decade, researchers and clinicians are still exploring the determinants that cause joint hypermobility to become symptomatic.

The symptoms of hypermobile patients can extend far beyond the confines of the musculoskeletal system,[61] as depicted in Figure 1 (right side of symptomatic hypermobility iceberg). Approximately two-thirds of patients with symptomatic hypermobility also report various functional multisystemic symptoms,[61] including, but not limited to, gastrointestinal dysfunction, orthostatic intolerance,[62] postural orthostatic tachycardia syndrome, urogynecological problems, symptoms of mast cell activation, physical and cognitive fatigue, and anxiety and depression,[63–68] constituting a syndromic presentation. At present, there is an association between GJH and many of these conditions, but it remains unknown if the same underlying pathology drives some or all the reported multisystemic features, or if they result from other associated factors such as deconditioning or chronic widespread pain and chronic fatigue, which are nonspecific symptoms.[7]

Some proposed pathogeneses link joint hypermobility to other multisystemic conditions. For example, orthostatic intolerance may be attributed to an increased vascular distensibility based on altered connective tissue or to peripheral small fiber neuropathy,[69] whereas gastrointestional disorders are linked to autonomic dysfunction/dysmotility, interoceptive sensitivity, and/or altered stretch and mechanoreceptor function of the intestines.[63] The pathogenesis of an association between mast cell activation and joint hypermobility is yet to be determined.[70]

The mechanisms behind the complex pain states that can be observed in this latter subgroup of hypermobile individuals are poorly understood.[21,71] Subsequent lesions of capsuloligamentous and other soft tissues may occur in conjunction with irritation of peripheral nerves due to compression, elongation, or entrapment,[54,57] which are some of the mechanisms proposed. The symptom profile may vary widely between patients as illustrated by the Spider chart (Fig. 2),[72] with symptoms presenting on a broad spectrum of severity.[73]

If a hypermobile patient also demonstrates several orthopedic deformities and skin abnormalities and vascular fragility and

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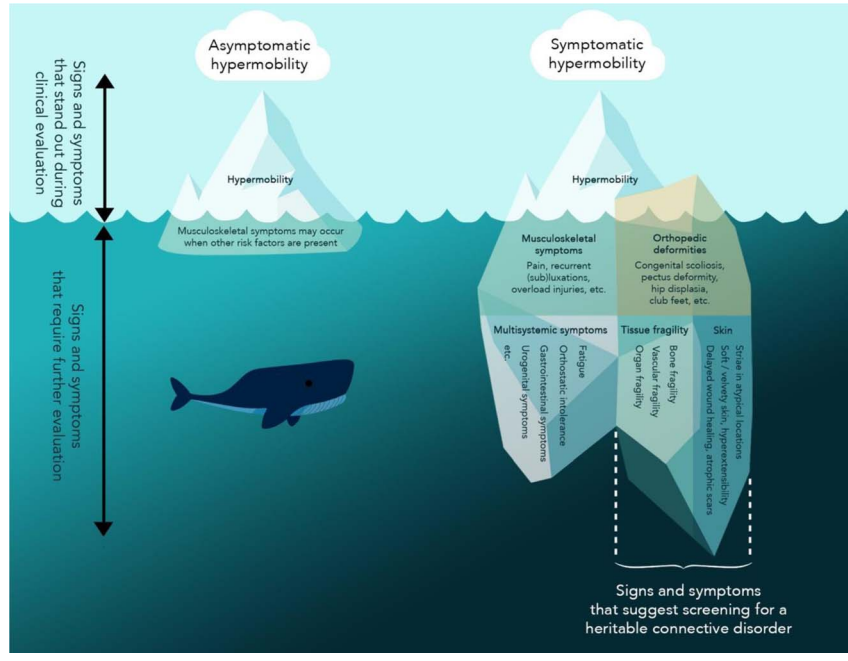


FIGURE 1. Phenotypic presentation of joint hypermobility. As a useful illustration, joint hypermobility can be compared with "the tip of an iceberg" that is visible above the water surface, as it can be a striking feature that stands out during clinical assessment. Whereas most individuals remain asymptomatic (iceberg on the left), some patients develop symptoms (iceberg on the right). If a hypermobile patient demonstrates orthopedic deformities and skin alterations and reports multiple signs of tissue fragility, ruling out a heritable connective tissue disorder is important (right part of the right iceberg). Color online-figure is available at http://www.jclinrheum.com.

reports multiple signs of tissue fragility, screening for an underlying heritable condition is warranted to ensure proper medical follow-up and avoid more severe complications. Examples of such pathologies are the heritable disorders of connective tissue such as Marfan syndrome, EDSs, osteogenesis imperfecta, and Stickler syndrome. Several other chromosomal disorders such as Down syndrome and metabolic disorders such as homocystinuria and hyperlysinemia may also need to be excluded as part of the differential diagnosis. Features that alert the clinician to attribute signs and symptoms to a heritable syndrome are evidence of:

1. Tissue fragility: bone fragility (recurrent fractures), and/or soft tissue fragility (abdominal hernia, bladder, uterine, or bowel prolapse) or organ fragility (rupture of hollow organs). The most important to recognize is vascular fragility (easy bruising, bleeding tendency, vascular aneurysms, dilatations, or dissections) associated with Marfan syndrome, vascular EDS, familial thoracic aortic aneurysm, and so on.
2. Skin fragility and altered skin structure: soft and velvety skin surface, stretchy skin, skin hyperextensibility, atrophic scarring, the presence of multiple scars, delayed wound healing, wound dehiscence, and so on.
3. Orthopedic deformities: pectus deformity, congenital club feet, short or tall stature, congenital scoliosis, bilateral congenital hip dysplasia and/or hip dislocations, increased arm span to length ratio, arachnodactyly, and so on.

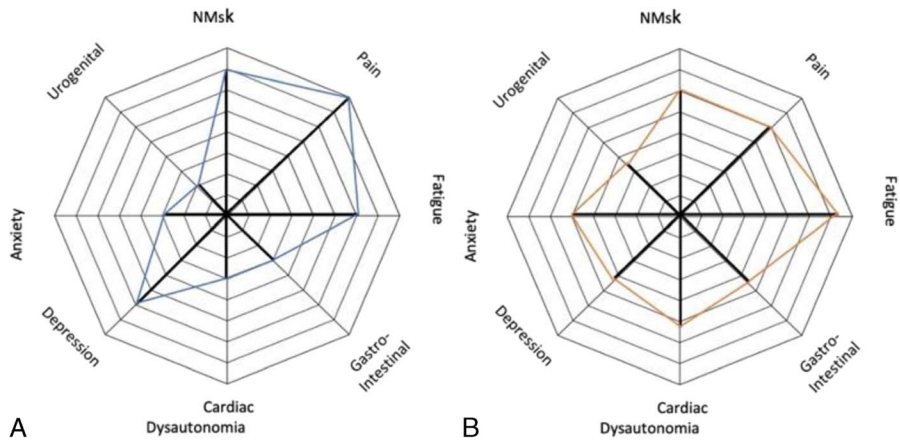


FIGURE 2. Example of heterogeneous multisystem symptom presentations in 2 patients diagnosed with hEDS. The distance from the center of the web denotes the severity of the symptom. Patient A predominantly experiences neuromuscular symptoms and pain. The symptoms of patient B suggest a more global presentation of symptoms. Color online-figure is available at http://www.jclinrheum.com.

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G-HSD and hEDS

Consistent diagnostic terminology and standardized, valid assessments are important enablers for research, evidence-informed treatments, and communication between health providers and patients. We have presented hypermobility terminology, variable presentations, sign and symptoms of GJH, and how it is assessed. Through this exploration, we have highlighted the diagnostic labels currently adopted.

The previous diagnoses of JHS or EDS–hypermobility type, essentially considered the same condition,[6] were revised in 2017. The revised 2017 EDS classification reports that for individuals with otherwise unclassified joint hypermobility, the term hEDS should be restricted to those with features suggestive of a systemic and/or Mendelian connective tissue disorder.[74] Based on a population study of health care records in Wales,[75] the prevalence of JHS, likely a combination of those currently diagnosed with hEDS and G-HSD, is 1 in 500 to 600.[76] Of the 13 types of EDSs, hEDS is the most common accounting for greater than 95% of all EDS presentations to specialist clinics.[77] The conditions G-HSD and hEDS share many clinical characteristics, including GJH, joint instability, and widespread chronic pain, all of which are included in the criteria for both diagnoses (https://www.ehlers-danlos.com/heds-diagnostic-checklist). The new diagnostic labels of hEDS and G-HSD have caused some confusion between researchers, clinicians, and those with a lived experience of these conditions, and from a symptom-management perspective, the 2 conditions can be managed identically. The heterogeneous presentation of multisystem signs and symptoms depicted in Figure 2 means that management must be individualized. Most pertinent to management is that thorough history-taking and clinical assessment must combine with equally thorough clinical reasoning, informed by patient expectations and goals.

Currently, the hEDS diagnostic criteria are not valid for use in children and adolescents as multiple multisystemic features that comprise criterion 2 of the 2017 classification are not appropriate in the assessment of children. For example, atrophic scarring cannot be seen in a young child who has not had a skin tear, and dental crowding cannot be determined in a child who has not yet had all adult teeth erupted. In light of these difficulties applying the current criteria to children, the development of pediatric specific criteria is underway led by the Pediatric Working Group of the International Consortium on EDS and HSD. Until that time, children should be monitored to document changes in GJH and other potentially associated multisystemic features until skeletal maturity is reached, at which time a diagnostic label such as hEDS can be reevaluated using diagnostic adult criteria.

Depending on the geographical location, the medical professionals best placed to oversee the multidisciplinary management of patients based on their individual presentation are clinical geneticists, rheumatologists, rehabilitation physicians, or pediatricians (for children/adolescents). These specialists will then confer with the patients' general practitioner and refer on to appropriate allied health or other specialists, and clinics with specific expertise (e.g., chronic pain).

CLINICAL IMPLICATIONS AND RESEARCH DIRECTIONS

The heterogeneity of measurement outcomes reported in the literature has hindered attempts to produce clinical assessment and management guidelines. The EDS Society is currently collating self-report and objective outcome measures (common data elements) including those appropriate for hypermobility assessment to standardize their use in this population globally.

While joint hypermobility is most commonly asymptomatic warranting identification only for risk surveillance and management, task-specific injury prevention, or performance enhancement,[78] this form of hypermobility does not need to be medicalized. In these cases, the Beighton score functions well to screen. However, in those who experience symptoms associated with their joint hypermobility, more extensive assessment to determine the joint(s) and plane(s) of movement affected together with patient-specific and objective functional assessments will permit targeted management. For example, a patient who describes shoulder instability and tests positive to all 3 ULHAT shoulder tests (Supplemental Table, http://links.lww.com/RHU/A464) and demonstrates functional movement impairments may best be managed with exercises that improve strength and control in more than 1 anatomical plane.

Although focusing on a diagnosis is important, from a clinical/management perspective, the focus should be on the patient's individual symptom presentation. This review highlights the strengths and limitations of many of the contemporary assessment methods and prompts clinicians to consider how these assessments add value or align with the presenting complaints or treatment goals of the patient. It is possible that those diagnosed with G-HSD are undermanaged because of the perception that their condition is less severe than hEDS. Large, cross-sectional and prospective studies are needed to determine whether there are phenotypic differences between the 2 cohorts if they exist and whether they should be managed similarly.

Finally, future research is warranted to validate diagnostic criteria, self-report, and physical measures in the pediatric population. Such research will need to incorporate standardized outcome measures on homogenous patient cohorts to enable the development of best-practice guidelines for children with symptomatic hypermobility.

CONCLUSIONS

Joint hypermobility presents on a spectrum from an asymptomatic physiological phenomenon through to 1 component of a complex myriad of multisystem presentations. This article has presented the current state of the science and research relating to the terminology, etiology, presentation, assessment, diagnosis, and future directions for research.

KEY POINTS

- Using standardized terminology about joint hypermobility will assist researchers to compare findings related to prevalence, diagnostics, and management.
- Joint hypermobility presents on a spectrum from an asymptomatic physiological phenomenon through to 1 component of multisystem presentations.
- Whereas joint hypermobility is often asymptomatic, symptomatic forms require specialized assessment, management, and follow-up.

ACKNOWLEDGMENTS

The authors thank the entire EDS Society and the International Consortium on EDS and HSD for their support of this review project and specifically Dr Alan Hakim, consultant rheumatologist, London, United Kingdom; Dr Fransiska Malfait, geneticist, Ghent University Hospital, Belgium; and Dr Louise Tofts, pediatric rehabilitation specialist, The Children's Hospital at Westmead, Sydney, Australia; for their valuable contribution to the review of this article. This review was written on behalf of

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the Allied Health Professionals Working Group of the International Consortium on EDS and HSD (https://www.ehlers-danlos.com/international-consortium-working-groups/#allied-health-working-group). They also acknowledge all the clinicians and researchers who have invested their energies to improve knowledge in this field and to improve diagnosis and management for people with symptomatic joint hypermobility and whose work is included and reflected in this review article.

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