
Hypermobility, the Ehlers-Danlos syndromes and chronic pain

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ABSTRACT

Chronic widespread pain is a common complaint among individuals affected by generalised joint hypermobility. In the absence of other conditions that cause chronic pain, these individuals are usually diagnosed with joint hypermobility syndrome (JHS). JHS is a multifactorial trait with a strong genetic basis, but no specific genetic markers. Clinical overlap of JHS is seen with heritable connective tissue disorders, particularly with the Ehlers-Danlos syndrome, hypermobile type (hEDS). The Ehlers-Danlos syndromes (EDS) comprise a heterogeneous group of rare monogenic conditions that are characterised by joint hypermobility, skin and vascular fragility and generalised connective tissue friability, and are caused by genetic defects in an array of extracellular matrix genes. The genetic basis of hEDS remains however unknown, in contrast to other well-described EDS subtypes. In view of the considerable clinical overlap with JHS, many consider it and hEDS to be a single clinical entity. Clinical experience and a limited number of clinical studies show that chronic pain also is common in EDS patients, especially in hEDS. The specific underlying causes and mechanisms of pain in JHS and EDS remain poorly understood. Factors likely contributing to the generation and chronicity of pain include nociceptive pain, directly based on structural changes in affected joints, muscle and connective tissue; neuropathic pain; impaired proprioception and muscle weakness; and central sensitisation. These mechanisms are not mutually exclusive, and likely more than one mechanism may be present. Furthermore, anxiety, depression, and other variables may influence the phenotype. Chronic pain in JHS and EDS patients often is inadequately controlled by traditional analgesics and physical therapy. In view of the high prevalence of these underrecognised conditions, future studies addressing

the nature and mediators of chronic pain are needed in order to potentially identify novel targets for therapeutic intervention and optimise treatment.

Hypermobility, joint hypermobility syndrome and Ehlers-Danlos syndromes

Joint hypermobility (JH) implies a range of joint movement that exceeds what is considered to be normal for that joint, taking into account the individual's age, gender and ethnicity. JH can be limited to one or a few joints (localised JH), but when present at multiple sites the term generalised JH (GJH) is preferred (1). The presence of GJH traditionally is defined by a score of at least 5 on the nine-point Beighton scale, a standardised test consisting of five clinical maneuvers (described in Table I) (2, 3). JH is a multifactorial trait with a strong genetic basis: in a female twin study, the heritability of JH was estimated to be 70% (4). A review article reports prevalence of GJH between 6 and 57% for women and 2–35% for men of varying ages and ethnicities (5). Besides gender, age and ethnicity, environmental factors that influence JH include weight, training, trauma, surgery and various medical conditions.

JH does not necessarily lead to symptoms, and is not a disease, nor a permanent diagnosis. The first comprehensive description of symptomatic JH in the rheumatological literature is attributed to Kirk, Ansell and Bywaters in 1967. They coined the term 'hypermobility syndrome' (HMS) and defined it as 'the occurrence of musculoskeletal symptoms in a hypermobile, but otherwise healthy person' (6). Later, the recognition of the relatively benign prognosis of HMS in terms of life-threatening complications led to the use of the term 'benign joint hypermobility syndrome' (BJHS) or briefly, 'joint hypermobility syndrome' (JHS) (7). A set of clinical diagnostic criteria, the 'Brighton Criteria' was established, the major criteria

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Table I. Beighton score used for the evaluation of joint hypermobility.

	Negative	Unilateral	Bilateral
Passive dorsiflexion of the 5th finger >90°	0	1	2
Passive flexion of the thumbs to the forearm	0	1	2
Hyperextension of the elbows >10°	0	1	2
Hyperextension of the knees >10°	0	1	2
Forward flexion of the trunk with knees fully extended and palms resting on the floor	0	Present	1

Table II. Brighton Criteria for Joint Hypermobility Syndrome (JHS) (8) and Villefranche Criteria for Hypermobile EDS (hEDS) (11).

<u>Brighton Criteria (JHS)</u>	<u>Villefranche Criteria for hEDS</u>
<p>Major Criteria</p> <ul style="list-style-type: none"> - Beighton score ≥ 4/9 (currently or historically) - Arthralgia > 3 months in > 4 joints <p>Minor Criteria</p> <ul style="list-style-type: none"> - Beighton score of 1-3 - Arthralgia in 1-3 joints or back pain, spondylosis, spondylolysis or spondylolisthesis - Dislocations/subluxations in more than 1 joint, or in 1 joint on more than one occasion - Soft tissue rheumatism ≥ 3 lesion (e.g. epicondylitis, tenosynovitis, bursitis) - Marfanoid habitus - Skin striae, hyperextensibility, thin skin, papyraceous scarring - Eye signs: drooping eyelids or myopia or anti-mongolid slant - History of varicose veins, hernias, uterine/rectal prolapses <p>For a diagnosis of JHS, the presence of both major criteria, one major and two minor, four minor, or two minor criteria plus one or more first-degree affected relative(s) is needed. The diagnosis of JHS needs clinical and/or molecular exclusion of overlapping heritable connective tissue disorders.</p>	<p>Major Criteria</p> <ul style="list-style-type: none"> - Beighton score ≥ 5/9 - Skin involvement (hyperextensibility and/or smooth, velvety skin) <p>Minor Criteria</p> <ul style="list-style-type: none"> - Recurring joint dislocations - Chronic joint/limb pain (> 3 months) - Positive family history <p>A major criterion has high diagnostic specificity and the presence of one or more major criteria is either necessary for clinical diagnosis or highly indicative. A minor criterion is a sign of lesser diagnostic specificity. The presence of one or more minor criteria contributes to the diagnosis. However, in the absence of major criteria they are not sufficient to establish the diagnosis</p>

being the presence of GJH and chronic musculoskeletal pain (8). Besides GJH and pain, it was recognised that JHS patients show mild signs of connective tissue fragility and laxity, including skin hyperextensibility, hernia, varicose veins, uterine or rectal prolapse and marfanoid habitus (Table II). As such, JHS shows overlap with several heritable connective tissue disorders (HCTD), such as Marfan syndrome and osteogenesis imperfecta, but most notably with the Ehlers-Danlos syndromes (EDS). JHS is sometimes considered a mild form of HCTD, but no specific genetic markers have been identified to date (7, 9).

EDS comprises a genetically and phenotypically heterogeneous group of monogenic disorders, mainly affecting the soft connective tissues. The major

clinical characteristics of EDS include skin hyperextensibility and fragility; vascular fragility with easy bruisability and a variable bleeding tendency; joint hypermobility (usually generalised) and manifestations of generalised connective tissue fragility (10). Depending on the EDS subtype and the underlying genetic defect, these manifestations and their consequences may vary from almost subclinical to severely debilitating and even life-threatening.

In 1997 six main EDS subtypes were defined, including the classical, vascular, hypermobility, kyphoscoliosis, arthrochalasia and dermatosparaxis subtype, and clinical diagnostic criteria were established for each of these subtypes (known as the ‘Villefranche Classification for EDS’). Most of these conditions were shown to be caused by

biochemical and/or molecular defects in fibrillar collagen types I, III and V, or in their modifying enzymes, making EDS an exemplary heritable collagen disorder (11). With the advent of next generation sequencing techniques, molecular defects have recently been identified in a variety of extracellular matrix (ECM) molecules, gradually expanding the list of distinct EDS subtypes, and increasing our understanding of the underlying pathogenetic basis of EDS. These studies have recently led to a revision of the EDS classification, which now includes 13 distinct clinical EDS subtypes, for which molecular defects have been identified in 19 different genes (Table III). Besides defects in fibrillar collagens (collagen types I, III and V), their modifying enzymes (ADAMTS-2, lysylhydroxylase 1 (LH1)), and molecules involved in collagen folding (FKBP22), defects have now also been identified in other constituents of the ECM (e.g. Tenascin-X, collagen type XII), enzymes involved in glycosaminoglycan biosynthesis (galactosyltransferase I and II (β4GalT7 and β3GalT6), dermatan 4-O-sulfotransferase-1 (D4ST1), dermatan sulfate epimerase (DSE)), (putative) transcription factors (ZNF469, PRDM5), components of the complement pathway (C1r, C1s) and an intracellular Zinc transporter (ZIP13) (12). Despite advances in our understanding of the genetic basis of EDS, one of the initially recognised and most prevalent EDS subtypes, hypermobile EDS (hEDS), remains molecularly unexplained. hEDS shows considerable clinical overlap with JHS, as reflected in the two sets of diagnostic criteria that have been used over the past two decades (Table II) (8, 11). The similarities between these conditions have created the notion that JHS and hEDS may constitute a single pathological entity (7, 13). Both conditions lack specific genetic profiles by which the diagnosis can be confirmed, and, as a result, researchers and clinicians have struggled with the terms JHS and hEDS over the decades, and they have often been used interchangeably, both in routine clinical care and in clinical research studies (13, 14).

The recently published revised EDS

Table III. The 2017 revised classification of the Ehlers-Danlos syndromes, inheritance pattern, and genetic basis (12).

EDS subtype	Abbreviation	IP	Gene	Protein
Classical EDS	cEDS	AD	Major: <i>COL5A1, COL5A2</i> Rare: <i>COL1A1</i>	Type V collagen Type I collagen
Classical-like EDS	clEDS	AR	<i>TNXB</i>	Tenascin-X
Cardiac-valvular EDS	cvEDS	AR	<i>COL1A2</i>	Type I collagen
Vascular EDS	vEDS	AD	Major: <i>COL3A1</i> Rare: <i>COL1A1</i>	Type III collagen Type I collagen
Hypermobile EDS	hEDS	AD	Unknown	Unknown
Arthrochalasia EDS	aEDS	AD	<i>COL1A1, COL1A2</i>	Type I collagen
Dermatosparaxis EDS	dEDS	AR	<i>ADAMTS2</i>	ADAMTS-2
Kyphoscoliotic EDS	kEDS	AR	<i>PLOD1</i> <i>FKBP14</i>	LH1 FKBP22
Brittle Cornea Syndrome	BCS	AR	<i>ZNF469</i> <i>PRDM5</i>	ZNF469 PRDM5
Spondylodysplastic EDS	spEDS	AR	<i>B4GALT7</i> <i>B3GALT6</i> <i>SLC39A13</i>	β4GalT7 β3GalT6 ZIP13
Musculocontractural EDS	mcEDS	AR	<i>CHST14</i> <i>DSE</i>	D4ST1 DSE
Myopathic EDS	mEDS	AD or AR	<i>COL12A1</i>	Type XII collagen
Periodontal EDS	pEDS	AD	<i>C1R</i> <i>C1S</i>	C1r C1s

IP: inheritance pattern; AD: autosomal dominant; AR: autosomal recessive.

nosology has addressed this inconsistency and has regrouped both conditions within the hypermobile type of EDS, with a much better-defined set of clinical criteria (12). The terms HMS and JHS are abandoned and replaced by the term ‘hypermobility spectrum disorders’ (HSD). HSD is intended as an alternative label for patients with symptomatic JH who do not have any rare form of EDS or who do not meet the new criteria for hEDS (12, 15, 16). This review discusses published studies that still used the ‘old’ JHS and hEDS terminology and criteria, hence the term JHS, and not HSD, is used throughout the manuscript

The natural history of pain in JHS and EDS

Due to the compromised structural integrity of the connective tissues, patients suffering from EDS and JHS are prone to joint instability, leading to joint dislocations (full displacements and subluxations), and articular and soft-tissue injuries. As a result, occasional acute and recurrent pain is a common manifestation of JH, which may evolve to chronic widespread musculoskeletal pain (17).

It has been estimated that among individuals with GJH, approximately 3.3% of women, and 0.6% of men develop chronic complaints (6, 18, 19). These incident rates may well be an underestimation, in view of the general unawareness of clinicians regarding GJH-related pain (20). Among EDS patients, chronic widespread pain is quite common. In 1997, Sacheti *et al.* interviewed 51 patients with different types of EDS, and found an incidence of chronic pain of 90%. This was the first published report to recognise that moderate to severe pain is common in EDS, starts early in life and progresses over time (21). A similar incidence was found in a more recent study by Voermans *et al.*, in a cohort of 273 EDS patients affected by various EDS types. In addition, this study showed a higher prevalence of pain in hypermobile than in classic EDS (cEDS), a correlation between pain severity and hypermobility, dislocations, previous surgery and nocturnal sleep quality, and that the pain contributes to functional impairment in daily life in many patients (22). These reports echo clinical experience that chronic, generalised musculoskeletal pain is the most frequent complaint of patients affected

by EDS, especially within the hEDS group, and the primary reason for seeking medical help. Nevertheless, further large clinical studies on the prevalence, natural history and characteristics of EDS-related pain are needed.

Most studies on EDS pain have subsequently focused on hEDS. Moreover, as discussed, several of these studies do not distinguish between hEDS and JHS, and consider these a single clinical entity (13, 14).

In our clinical experience and those of others, pain in JHS and hEDS usually starts early in life, either during childhood or in young adulthood (15, 23-26). It is often triggered by apparent external factors such as injury, surgery, sport activities, psychological distress or various comorbidities (25). At first, pain is often felt as an acute and localised symptom, in relation to joint trauma, such as dislocations and sprains (27, 28) or as “growing pains”.

Muscle cramps, periarticular inflammation, enthesopathies, such as tendinitis, tenosynovitis and fasciitis, and nerve entrapment syndromes can add to the localised musculoskeletal pain (28-30). In later stages of life, pain becomes widespread. Arthralgias and myalgias are the most common pain presentations in young adult and adult patients (22). The pain is most frequently localised in neck, shoulders, forearms, fingers, hips, knees and feet, likely reflecting the musculoskeletal pain pattern (22, 28). At first, pain may be limited to a few joints and/or muscles and have a migratory pattern, but it gradually becomes more persistent and assumes a more generalised distribution. Once pain becomes widespread, patients often lose the ability to localise its exact origin and exacerbating and relieving factors. Common additional complaints in this stage include burning sensations, peripheral paresthesias, generalised hyperalgesia, allodynia and hypersensitivity to various stimuli, such as light, sound and odors (29, 31-33). Besides musculoskeletal pain, patients with JHS and hEDS often report pain in non-articular regions such as headaches (21, 24, 28, 34, 35), gastro-intestinal (24, 36), genito-urinary and pelvic pain (37, 38). Accompanying the chronic, wide-

spread pain is often severe fatigue, seen in up to 84% of patients with JHS/hEDS (39). This fatigue can be sufficiently substantial to meet criteria for chronic fatigue syndrome (40). The underlying cause is unclear and likely multifactorial, but muscle weakness (41, 42), sleep disturbance due to nocturnal pain (22), concentration problems (39) and cardiovascular dysautonomia (43-46) may be contributing factors.

The chronic, widespread pain in JHS/hEDS is associated with high use of analgesics, surgery and physical therapy (22, 47). Nonetheless, it is generally refractory to these interventions; consequently it often has a detrimental effect on physical, social and emotional function in affected individuals, with a substantial deterioration of their quality of life (23). Psychological dysfunction and emotional problems are common, including depression and anxiety (28, 48-52).

The pathogenesis of pain in hypermobility and EDS

The specific underlying causes and mechanisms of pain in JHS and EDS patients remain poorly understood. No pathophysiological model has been identified yet, although evidence has been presented for several types of mechanisms, including nociceptive and neuropathic components, as well as pain sensitisation, as seen in musculoskeletal pain of many aetiologies. Furthermore, more than one aetiology may often be involved, as is seen in many pathological entities.

Nociceptive pain directly related to affected ligaments and tendons, joints, muscles and connective tissue, is frequently encountered, and often presents at early stages of acute and localised pain. Joint instability due to congenital capsuloligamentous laxity predisposes patients to dislocations and to repetitive soft-tissue traumas, such as ligamentous and tendinous overstretching and tears (21, 22, 53). In addition, microtraumata may cause subclinical damage that is often not supported by a recognised history of joint trauma. The occurrence of microtraumata on joint surfaces may lead to adaptation and compensation of movement and gait patterns, conse-

quently causing overload in other areas of the movement apparatus (25, 54). Other contributors to nociceptive pain may include multiple surgical procedures (22), reduced bone mass (55-57) and premature osteoarthritis (58); the impact of the latter two on the phenotype of JHS/hEDS however remains a matter of debate.

Besides nociceptive pain, several studies support a neuropathic component for EDS-related pain. A questionnaire study by Camerota *et al.*, suggested that about 60% of hEDS and cEDS participants had 'at least probable' neuropathic pain (31). Voermans *et al.* provided evidence for compression and axonal neuropathies in various EDS types (59). Recently, an increased rate of upper limb nerve (sub)luxations was demonstrated in JHS/hEDS, which may contribute to some peripheral neuropathic features of pain, such as paresthesias (29). Henderson *et al.* reported that laxity of the cervical spine can lead to direct compression of the spinal cord (60). Recently, a decreased intraepidermal nerve fibre density was demonstrated in skin biopsies derived from EDS/JHS patients, providing evidence for the existence of small fibre neuropathy (61, 62).

In addition to these nociceptive and neuropathic components, an important role for central sensitisation in the chronification of generalised pain has been found in many individuals with JHS and hEDS. The earliest reports concerning central sensitisation emerged from studies indicating evidence for generalised hyperalgesia in patients with these conditions (32, 33, 63). Unpublished data from our research group in a cohort of hEDS/JHS patients provide further evidence for central sensitisation, by showing increased wind-up to repeated stimuli and decreased exercise-induced analgesia (64).

Two important modifiers have been proposed to play a role in the generation of chronic pain: lack of proprioceptive acuity and muscle weakness. Several studies have demonstrated impaired proprioception in JHS and EDS subjects (65-71). As proprioception is essential for joint stabilisation, patients

with JH may have an increased risk for injury. Muscle weakness, likely related to muscle hypotonia, has also been observed and may be partly due to the increased laxity of the tendons, which cannot normally transmit the power produced by muscle. In addition, the fear of provoking pain and injury may lead to decreased levels of activity, ultimately resulting in deconditioning and exercise intolerance (42).

Psychological influences are important in an individual's experience of a painful stimulus, modifying the risk, perception, and response to acute pain and the risk to develop chronic pain. Pain is intimately related to fear and anxiety. In the literature on chronic pain, the fear-avoidance model may explain in part the disabling role of pain-related fear in many patients. It states that a highly fearful person learns to avoid activities that he or she perceives as harmful or pain-provoking (72). Evidence for pain-related fear in hypermobile subjects was provided by Rombaut *et al.*, who reported fear of falling among women with JHS/hEDS (73), and Celletti *et al.* who reported that kinesiophobia is a common symptom in JHS/hEDS (74, 75). Over the long term, avoidance behavior that results from fear of pain leads to disuse and muscle deconditioning, which generates further loss of muscle strength and flexibility. This often aggravates functional disability and leads to depression, which in turn reduces pain tolerance and promotes further pain (76). Besides avoidance strategies, other emotional and cognitive mechanisms likely contribute to chronic pain in EDS and JHS (25).

The extremely high prevalence of chronic musculoskeletal pain in patients with EDS and with other HCTD leads one to hypothesise that abnormalities in the ECM can contribute to the generation and chronification of pain (77). The ECM is composed of structural and non-structural proteins, such as fibrillar proteins (collagens), glycoproteins (fibronectin, tenascins) and several classes of proteoglycans (heparan sulfate, chondroitin/dermatan sulfate and keratan sulfate proteoglycans) embedded in a hydrogel matrix. A clear role

has been demonstrated for the ECM in general nociception; for instance, functional deficits have been observed in peripheral nerves of collagen type VI deficient mice, which were paralleled by impaired nociception because of disorganised C-fibre nociceptors (78). Moreover, painful injuries have been shown to induce unique ECM alterations at acute and chronic time points after the injury, such as elevation of matrix metalloproteinase (MMP) levels resulting in microglial activation (79), and alterations in integrin signaling (80). Furthermore, the ECM has been demonstrated to be a key player in central nervous system (CNS) neuroplasticity and connectivity (77).

Patients with EDS harbour defects in different components of the ECM, including collagens, glycoproteins and proteoglycans (Table III) (12). The resulting abnormalities in connective tissue integrity and functioning could have a devastating impact on the nervous system. These proteins, such as collagen types I, III, V, tenascins and proteoglycans as well as their receptors, are distributed throughout the connective tissue of the central and peripheral nervous system and play important structural and functional roles (81).

Connective tissue allows the body to sense tensile and compressive forces and pressure (*e.g.*, proprioception, pain perception), enabling the individual to react appropriately with a protective response. Hence, the defective ECM in EDS might compromise the formation of the (peripheral) nervous system and contribute to the increased vulnerability of peripheral nerves to stretching or pressure (59).

Many cases of chronic widespread pain evolve from local nociceptive and neuropathic musculoskeletal problems, characterised by a period of massive peripheral input in the (sub)acute to chronic stage (82). In response, the central nervous system modulates the sensitivity of the somatosensory system. Once central sensitisation is established, it is sustained or aggravated by new peripheral input (83). In EDS, central sensitisation may arise as a consequence of the continuous stimulation of peripheral nociceptors by media-

tors released from the aberrant ECM. It has been reported that a variety of sequestered ECM components can act as damage-associated molecular patterns (DAMPs) (84), which function as endogenous danger signals and are recognised by pattern recognition receptors (PRRs) of the immune system. Recently it has been demonstrated that sensory neurons can express the same PRRs (*e.g.* toll-like receptors (TLRs), which can induce painful pathways upon activation (85-87). As such, it could be hypothesised that the abnormal ECM associated with EDS is a potential source of DAMPs, which can chronically stimulate peripheral nociceptors, thereby leading to sensitisation and driving pain.

Overall, it is clear that several types of pain etiology coexist in JHS/EDS patients, based on the contribution of nociceptive, neuropathic, and sensitisation mechanisms and that multiple biological and psychological factors contribute to the evolving pain phenotype. In addition, there are many genetic and environmental factors that contribute to pain development. Genetic determinants of variability in pain sensitivity for instance, that are independent of the degree of joint hypermobility, could influence the pain phenotype. Studies investigating pain thresholds in healthy individuals highlight a prominent role for common genetic variations in proteins involved in various aspects of pain neurotransmission (88, 89).

Given the complex nature of pain in JHS and EDS patients, our fragmented understanding of the mechanisms underlying pain, and the absence of reports on effectiveness of treatment modalities in large cohorts, management of acute and chronic pain in these patients is challenging and currently insufficient (26). It requires a patient-tailored and multidisciplinary approach, combining pharmacological intervention with physical and psychological therapy, in order to treat the causes of pain and minimize the pain sensation, with a common goal to improve quality of life and daily functioning. Management of JHS and EDS-related pain has excellently been reviewed in several recent papers (25, 26, 90, 91).

Conclusion

Chronic widespread pain is an important and underrecognised complaint in individuals displaying generalised joint hypermobility. The majority of these individuals are diagnosed with JHS, a multifactorial condition with a strong genetic basis. Although the specific genetic basis of JHS has not been elucidated, JHS shows signs of generalised connective tissue fragility, and as such overlaps with the HCTD, especially the Ehlers-Danlos Syndromes. These monogenic disorders result from molecular defects in constituents of the ECM, and chronic widespread pain is a major complaint in many EDS patients as well. The specific underlying causes and mechanisms of pain in these patients are not well understood. Nociceptive pain, neuropathic pain and central sensitisation all contribute to the evolving pain phenotype. Like for other chronic pain conditions, genetic factors (*e.g.*, in genes encoding connective tissue proteins and/or genes involved in pain neurotransmission), environmental factors, but also psychological and emotional factors have been proposed to influence the pain phenotype.

Management of the often severe, changing and highly debilitating pain in hypermobile patients is currently insufficient. Traditional pain medications do not adequately treat most patients, probably because the underlying mechanisms are different and/or more complex than for most other pain conditions.

As EDS arises from genetic defects in diverse components of the ECM, it provides a unique model to study the pathophysiological connection between the ECM and pain. This could help to identify mediators and pathways that initiate and/or maintain pain in EDS patients, and the mechanisms by which these affect molecular and/or cellular changes in the nervous system. Collectively, this knowledge might expose possible analgesic targets. In the long run, these insights might not only be beneficial for EDS patients, but will also shed more light on more common chronic musculoskeletal pain conditions, including JHS, but also fibromyalgia and osteoarthritis.

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References

- HAKIM A, GRAHAME R: Joint hypermobility. *Best Pract Res Clin Rheumatol* 2003; 17: 989-1004.
- BEIGHTON P, SOLOMON L, SOSKOLNE CL: Articular mobility in an African population. *Ann Rheum Dis* 1973; 32: 413-8.
- JUUL-KRISTENSEN B, SCHMEDLING K, ROMBAUT L, LUND H, ENGELBERT RHH: Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. *In: TINKLE BT, MALFAIT F, FRANCOMANO CA, BYERS PH (Eds.): Am J Med Genet C Semin Med Genet* 2017; 175: 116-47.
- HAKIM AJ, CHERKAS LF, GRAHAME R, SPECTOR TD, MACGREGOR AJ: The genetic epidemiology of joint hypermobility: a population study of female twins. *Arthritis Rheum* Wiley Subscription Services, Inc., A Wiley Company; 2004;50:2640-4.
- REMVIG L, JENSEN DV, WARD RC: Epidemiology of general joint hypermobility and basis for the proposed criteria for benign joint hypermobility syndrome: review of the literature. *J Rheumatol* 2007; 34: 804-9.
- KIRK JA, ANSELL BM, BYWATERS EG: The hypermobility syndrome. Musculoskeletal complaints associated with generalized joint hypermobility. *Ann Rheum Dis* 1967; 26: 419-25.
- GRAHAME R: Joint hypermobility and genetic collagen disorders: are they related? *Arch Dis Child* 1999; 80: 188-91.
- GRAHAME R, BIRD HA, CHILD A: The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* 2000; 27: 1777-9.
- MALFAIT F, HAKIM AJ, DE PAEPE A, GRAHAME R: The genetic basis of the joint hypermobility syndromes. *Rheumatology (Oxford)* 2006; 45: 502-7.
- STEINMANN B, POYCE P, SUPERTI-FURGA A: The Ehlers-Danlos Syndrome. Hoboken, NJ, USA: John Wiley & Sons; 2003. 431-523.
- BEIGHTON P, DE PAEPE A, STEINMANN B, TSIPOURAS P, WENSTRUP RJ: Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998; 77 :31-7.
- MALFAIT F, FRANCOMANO C, BYERS P *et al.*: The 2017 international classification of the Ehlers-Danlos syndromes. Tinkle BT, Malfait F, Francomano CA, Byers PH, editors. *Am J Med Genet C Semin Med Genet* 2017; 175: 8-26.
- TINKLE BT, BIRD HA, GRAHAME R, LAVALLEE M, LEVY HP, SILLENCE D: The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *Am J Med Genet A* 2009; 149A: 2368-70.
- CASTORI M, DORDONI C, VALLIANTE M *et al.*: Nosology and inheritance pattern(s) of joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type: A study of intrafamilial and interfamilial variability in 23 Italian pedigrees. *Am J Med Genet A* 2014; 164A: 3010-20.
- 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. Tinkle BT, Malfait F, Francomano CA, Byers PH, editors. *Am J Med Genet C Semin Med Genet* 2017; 175: 48-69.
- CASTORI M, TINKLE B, LEVY H, GRAHAME R, MALFAIT F, HAKIM A: A framework for the classification of joint hypermobility and related conditions. *Am J Med Genet C Semin Med Genet* 2017; 175: 148-57.
- HAKIM AJ, KEER R, GRAHAME R (Eds): Hypermobility, Fibromyalgia and Chronic Pain. Churchill Livingstone Elsevier, 2011: 1-332.
- MURRAY KJ: Hypermobility disorders in children and adolescents. *Best Pract Res Clin Rheumatol* 2006; 20: 329-51.
- SCHEPER MC, ENGELBERT RHH, RAMECKERS EAA, VERBUNT J, REMVIG L, JUUL-KRISTENSEN B: Children with generalised joint hypermobility and musculoskeletal complaints: state of the art on diagnostics, clinical characteristics, and treatment. *Biomed Res Int Hindawi* 2013; 69: 121054-13.
- GRAHAME R: Hypermobility: an important but often neglected area within rheumatology. *Nat Clin Pract Rheumatol* 2008; 4: 522-4.
- SACHETI A, SZEMERE J, BERNSTEIN B, TAFAS T, SCHECHTER N, TSIPOURAS P: Chronic pain is a manifestation of the Ehlers-Danlos syndrome. *J Pain Symptom Manage* 1997; 14: 88-93.
- VOERMANS NC, KNOOP H, BLEIJENBERG G, VAN ENGELEN BG: Pain in ehlers-danlos syndrome is common, severe, and associated with functional impairment. *J Pain Symptom Manage* 2010; 40: 370-8.
- ROMBAUT L, MALFAIT F, DE PAEPE A *et al.*: Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: a comparative study with fibromyalgia and rheumatoid arthritis. *Arthritis Rheum* 2011; 63: 1979-87.
- CASTORI M, CAMEROTA F, CELLETTI C *et al.*: Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: a pilot study on 21 patients. *Am J Med Genet A* 2010; 152A: 556-64.
- CASTORI M, MORLINO S, CELLETTI C *et al.*: Re-writing the natural history of pain and related symptoms in the joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet A* 2013; 161A: 2989-3004.
- CHOPRA P, TINKLE B, HAMONET C *et al.*: Pain management in the Ehlers-Danlos syndromes. Tinkle BT, Malfait F, Francomano CA, Byers PH, editors. *Am J Med Genet C Semin Med Genet* 2nd ed. 2017;175:212-9.
- AINSWORTH SR, AULICINO PL: A survey of patients with Ehlers-Danlos syndrome. *Clin Orthop Relat Res* 1993; 286: 250-6.
- ROMBAUT L, MALFAIT F, COOLS A, DE PAEPE A, CALDERS P: Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. *Disabil Rehabil* 2010; 32: 1339-45.
- GRANATA G, PADUAL L, CELLETTI C, CASTORI M, SARACENI VM, CAMEROTA F: Entrapment neuropathies and polyneuropathies in joint hypermobility syndrome/Ehlers-Danlos syndrome. *Clin Neurophysiol* 2013; 124: 1689-94.
- AKTAS I, OFLUOGLU D, ALBAY T: The relationship between benign joint hypermobility syndrome and carpal tunnel syndrome. *Clin Rheumatol* 2008; 27: 1283-7.
- CAMEROTA F, CELLETTI C, CASTORI M, GRAMMATICO P, PADUAL L: Neuropathic pain is a common feature in Ehlers-Danlos syndrome. *J Pain Symptom Manage* 2011; 41: e2-4.
- ROMBAUT L, SCHEPER M, DE WANDELE I *et al.*: Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: evidence for generalized hyperalgesia. *Clin Rheumatol* 2014; 34: 1121-9.
- SCHEPER MC, PACEY V, ROMBAUT L *et al.*: Generalized Hyperalgesia in children and adults diagnosed with Hypermobility Syndrome and Ehlers-Danlos Syndrome Hypermobility type: A discriminative analysis. *Arthritis Care Res (Hoboken)* 2017; 69: 421-9.
- BENDIK EM, TINKLE BT, AL-SHUIK E *et al.*: Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. *Cephalalgia* 2011; 31: 603-13.
- NEILSON D, MARTIN VT: Joint hypermobility and headache: understanding the glue that binds the two together – part 1. *Headache* 2014; 54: 1393-402.
- FIKREE A, AKTAR R, GRAHAME R *et al.*: Functional gastrointestinal disorders are associated with the joint hypermobility syndrome in secondary care: a case-control study. *Neurogastroenterol Motil* 2015; 27: 569-79.
- MCINTOSH LJ, STANITSKI DF, MALLETT VT, FRAHM JD, RICHARDSON DA, EVANS MI: Ehlers-Danlos syndrome: relationship between joint hypermobility, urinary incontinence, and pelvic floor prolapse. *Gynecol Obstet Invest* 1996; 41: 135-9.
- CASTORI M, MORLINO S, DORDONI C *et al.*: Gynecologic and obstetric implications of the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome hypermobility type) in 82 Italian patients. *Am J Med Genet A Wiley Subscription Services, Inc., A Wiley Company*; 2012; 158A: 2176-82.
- VOERMANS NC, KNOOP H, VAN DE KAMP N, HAMEL BC, BLEIJENBERG G, VAN ENGELEN BG: Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos Syndrome. *Semin Arthritis Rheum* 2010; 40: 267-74.
- CASTORI M, CELLETTI C, CAMEROTA F, GRAMMATICO P: Chronic fatigue syndrome is commonly diagnosed in patients with Ehlers-Danlos syndrome hypermobility type/joint hypermobility syndrome. *Clin Exp Rheumatol* 2011; 29: 597-8.
- VOERMANS NC, KNOOP H, BLEIJENBERG G, VAN ENGELEN BG: Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: an explorative study. *Physiotherapy* 2011; 97: 170-4.
- ROMBAUT L, MALFAIT F, DE WANDELE I *et al.*: Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers-Danlos syndrome. *Arthritis Care*

- Res (Hoboken) John Wiley & Sons, Inc; 2012;64:1584-92.
43. ROWE PC, BARRON DF, CALKINS H, MAUMENEE IH, TONG PY, GERAGHTY MT: Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 1999; 135: 494-9.
 44. GAZIT Y, NAHIR AM, GRAHAME R, JACOB G: Dysautonomia in the joint hypermobility syndrome. *Am J Med* 2003; 115: 33-40.
 45. HAKIM AJ, GRAHAME R: Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? *Rheumatology (Oxford)* 2004; 43: 1194-5.
 46. DE WANDELE I, ROMBAUT L, DE BACKER T et al.: Orthostatic intolerance and fatigue in the hypermobility type of Ehlers-Danlos Syndrome. *Rheumatology (Oxford)* 2016; 55: 1412-20.
 47. 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: 1106-12.
 48. BULBENA A, DURÓ JC, MATEO A, PORTA M, VALLEJO J: Joint hypermobility syndrome and anxiety disorders. *Lancet* 1988; 2: 694.
 49. BULBENAA, DURÓ JC, PORTA M et al.: Anxiety disorders in the joint hypermobility syndrome. *Psychiatry Res* 1993; 46: 59-68.
 50. LUMLEY MA, JORDAN M, RUBENSTEIN R, TSIPOURAS P, EVANS MI: Psychosocial functioning in the Ehlers-Danlos syndrome. *Am J Med Genet* 1994; 53: 149-52.
 51. MARTÍN-SANTOS R, BULBENA A, PORTA M, GAGO J, MOLINA L, DURÓ JC: Association between joint hypermobility syndrome and panic disorder. *Am J Psychiatry* 1998; 155: 1578-83.
 52. BAEZA-VELASCO C, GÉLY-NARGEOT MC, BULBENA VILARRASA A, BRAVO JF: Joint hypermobility syndrome: problems that require psychological intervention. *Rheumatol Int* 2011; 31: 1131-6.
 53. HUDSON N, FITZCHARLES MA, COHEN M, STARR MR, ESDAILE JM: The association of soft-tissue rheumatism and hypermobility. *Br J Rheumatol* 1998; 37: 382-6.
 54. FERRELL WR, TENNANT N, STURROCK RD ASHTON et al.: Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. *Arthritis Rheum* 2004; 50: 3323-8.
 55. DOLAN AL, ARDEN NK, GRAHAME R, SPECTOR TD: Assessment of bone in Ehlers Danlos syndrome by ultrasound and densitometry. *Ann Rheum Dis* 1998; 57: 630-3.
 56. NIJS J, VAN ESSCHE E, DE MUNCK M, DEQUEKER J: Ultrasonographic, Axial, and Peripheral Measurements in Female Patients with Benign Hypermobility Syndrome. *Calcif Tissue Int* 2000; 67: 37-40.
 57. GULBAHAR S, SAHIN E, BAYDAR M et al.: Hypermobility syndrome increases the risk for low bone mass. *Clin Rheumatol* 2006; 25: 511-4.
 58. JÓNSSON H, ELIASSON GJ, JONSSON A et al.: High hand joint mobility is associated with radiological CMC1 osteoarthritis: the AGES-Reykjavik study. *Osteoarthritis Cartilage* 2009; 17: 592-5.
 59. VOERMANS NC, KNOOPH, VAN ENGELEN BG: High frequency of neuropathic pain in Ehlers-Danlos syndrome: an association with axonal polyneuropathy and compression neuropathy? *J Pain Symptom Manage* 2011; 41: e4-6.
 60. HENDERSON FC, AUSTIN C, BENZEL E et al.: Neurological and spinal manifestations of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet* 2017; 175: 195-211.
 61. PASCARELLA A, PROVITERA V, LULLO F et al.: Evidence of small fiber neuropathy in a patient with Ehlers-Danlos syndrome, hypermobility-type. *Clin Neurophysiol* 2015; 127: 1914-6.
 62. CAZZATO D, CASTORI M, LOMBARDI R et al.: Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. *Neurology* 2016; 87: 155-9.
 63. 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: 1319-25.
 64. DE WANDELE I, HERMANS L, ROMBAUT L et al.: Endogenous pain modulation in the Ehlers-Danlos syndrome, hypermobility type. *Osteoarthritis Cartilage* 2014; 22: S409-10.
 65. MALLIK AK, FERRELL WR, McDONALD AG, STURROCK RD: Impaired proprioceptive acuity at the proximal interphalangeal joint in patients with the hypermobility syndrome. *Rheumatology (Oxford)* 1994; 33: 631-7.
 66. HALL MG, FERRELL WR, STURROCK RD, HAMBLIN DL, BAXENDALE RH: The effect of the hypermobility syndrome on knee joint proprioception. *Br J Rheumatol* 1995; 34: 121-5.
 67. FATOYE F, PALMER S, MACMILLAN F, ROWE P, VAN DER LINDEN M: Proprioception and muscle torque deficits in children with hypermobility syndrome. *Rheumatology (Oxford)* 2009; 48: 152-7.
 68. ROMBAUT L, DE PAEPE A, MALFAIT F, COOLS A, CALDERS P: Joint position sense and vibratory perception sense in patients with Ehlers-Danlos syndrome type III (hypermobility type). *Clin Rheumatol* 2010; 29: 289-95.
 69. CELLETTI C, CASTORI M, GALLI M et al.: Evaluation of balance and improvement of proprioception by repetitive muscle vibration in a 15-year-old girl with joint hypermobility syndrome. *Arthritis Care Res (Hoboken)* 2011; 63: 775-9.
 70. CLAYTON HA, CRESSMAN EK, HENRIQUES DYP: Proprioceptive sensitivity in Ehlers-Danlos syndrome patients. *Exp Brain Res* 2013; 230: 311-21.
 71. CLAYTON HA, JONES SAH, HENRIQUES DYP: Proprioceptive precision is impaired in Ehlers-Danlos syndrome. *Springerplus* 2015; 4: 323.
 72. VLAEYEN JW, LINTON SJ: Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain* 2000; 85: 317-32.
 73. ROMBAUT L, MALFAIT F, DE WANDELE I et al.: Balance, gait, falls, and fear of falling in women with the hypermobility type of Ehlers-Danlos syndrome. *Arthritis Care Res (Hoboken)* 2011; 63: 1432-9.
 74. GRAHAME R: Joint hypermobility syndrome pain. *Curr Pain Headache Rep* 2009; 13: 427-33.
 75. CELLETTI C, CASTORI M, LA TORRE G, CAMEROTA F: Evaluation of kinesiophobia and its correlations with pain and fatigue in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Biomed Res Int* 2013; 2013: 580460-7.
 76. SCHEPER MC, DE VRIES JE, VERBUNT J, ENGELBERT RH: Chronic pain in hypermobility syndrome and Ehlers-Danlos syndrome (hypermobility type): it is a challenge. *J Pain Res* 2015; 8: 591-601.
 77. TAJERIAN M, CLARK JD: The role of the extracellular matrix in chronic pain following injury. *Pain* 2015; 156: 366-70.
 78. CHEN P, CESCONE M, MEGIGHIAN A, BONALDO P: Collagen VI regulates peripheral nerve myelination and function. *FASEB J* 2014; 28: 1145-56.
 79. KAWASAKI Y, XU Z-Z, WANG X et al.: Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. *Nat Med* 2008; 14: 331-6.
 80. DINA OA, PARADA CA, YEH J, CHEN X, MCCARTER GC, LEVINE JD: Integrin signaling in inflammatory and neuropathic pain in the rat. *Eur J Neurosci* 2004; 19: 634-42.
 81. REICHARDT L, PROKOP A: Introduction: The role of extracellular matrix in nervous system development and maintenance. *Dev Neurobiol* 2011; 71: 883-8.
 82. NIJS J, VAN WILGEN CP, VAN OOSTERWIJCK J, VAN ITTERSUM M, MEEUS M: How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: Practice guidelines. *Man Ther* 2011; 16: 413-8.
 83. AFFAITATI G, COSTANTINI R, FABRIZIO A, LAPENNA D, TAFURI E, GIAMBERARDINO MA: Effects of treatment of peripheral pain generators in fibromyalgia patients. *Eur J Pain* 2011; 15: 61-9.
 84. SCHAEFER L: Complexity of danger: the diverse nature of damage-associated molecular patterns. *J Biol Chem* 2014; 289: 35237-45.
 85. QI J, BUZAS K, FAN H et al.: Painful pathways induced by TLR stimulation of dorsal root ganglion neurons. *J Immunol* 2011; 186: 6417-26.
 86. MILLER RE, BELMADANIA, ISHIHARA S et al.: Damage-associated molecular patterns generated in osteoarthritis directly excite murine nociceptive neurons through toll-like receptor 4. *Arthritis Rheumatol* 2015; 67: 2933-4.
 87. FELDMAN P, DUE MR, RIPSCH MS, KHANNA R, WHITE FA: The persistent release of HMGB1 contributes to tactile hyperalgesia in a rodent model of neuropathic pain. *J Neuroinflammation* 2012; 9: 180.
 88. ZUBIETA J-K, HEITZEG MM, SMITH YR et al.: COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 2003; 299: 1240-3.
 89. ZORINA-LICHTENWALTER K, MELOTO CB, KHOURY S, DIATCHENKO LB: Genetic predictors of human chronic pain conditions. *Neuroscience* 2016; 338: 36-62.
 90. 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: 2055-70.
 91. CASTORI M: Pain in Ehlers-Danlos syndromes: manifestations, therapeutic strategies and future perspectives. *Expert Opin Orphan Drugs* 2016; 4: 1145-58.