Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type

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REVIEW ARTICLE

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Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: A review for the gastroenterologist

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Abstract

Background: Joint hypermobility syndrome (JHS)/Ehlers-Danlos syndrome hypermobility type (EDS-HT) is the most common hereditary non-inflammatory disorder of connective tissue, characterized by a wide range of symptoms, mainly joint hyperextensibility and musculoskeletal symptoms. A majority of patients also experiences gastrointestinal (GI) symptoms. Furthermore, JHS/EDS-HT has specifically been shown to be highly prevalent in patients with functional GI disorders, such as functional dyspepsia and irritable bowel syndrome.

Purpose: The aim of this review was to examine the nature of GI symptoms and their underlying pathophysiology in JHS/EDS-HT. In addition, we consider the clinical implications of the diagnosis and treatment of JHS/EDS-HT for practicing clinicians in gastroenterology. Observations summarized in this review may furthermore represent the first step toward the identification of a new pathophysiological basis for a substantial subgroup of patients with functional GI disorders.

KEYWORDS
Ehlers-Danlos syndrome, functional dyspepsia, functional GI disorders, joint hypermobility syndrome

1 | INTRODUCTION

Joint hypermobility syndrome (JHS)/Ehlers-Danlos syndrome hypermobility type (EDS-HT) is presumably the most common hereditary non-inflammatory disorder of connective tissue laxity, mainly characterized by joint hyperextensibility in association with musculoskeletal symptoms. Joint hypermobility syndrome/EDS-HT is recognized as a multisystem disorder.[1] For instance, autonomic dysfunction, chronic pain syndromes, urinary dysfunction, anxiety and mood disorders, and structural disorders such as pelvic organ prolapse have been described in patients with JHS/EDS-HT[1] (see Figure 1) and occur more frequently in JHS/EDS-HT compared with age- and gender-matched healthy controls.[2] Notably, there is a high prevalence of gastrointestinal (GI) symptoms in patients with JHS/EDS-HT, such as epigastric discomfort, gastro-esophageal reflux, and constipation.[3–5] In one study, GI symptoms were reported to be particularly prominent in the patients with JHS/EDS-HT who also had high levels of fatigue, cutaneous changes, orthostatic, immune, urogynecological, visual, and respiratory problems, and reduced quality-of-life metrics.[6] However, there are considerable interindividual differences in the clinical presentation of JHS/EDS-HT, thereby complicating its diagnosis and management.[6]

It should be noted that although EDS-HT shows a significant phenotypic overlap with the JHS, overall consensus regarding the exact relation between these syndromes is currently lacking, mainly because their genetic background is incompletely understood.[7,8] To date, there are three different opinions concerning the overlap between

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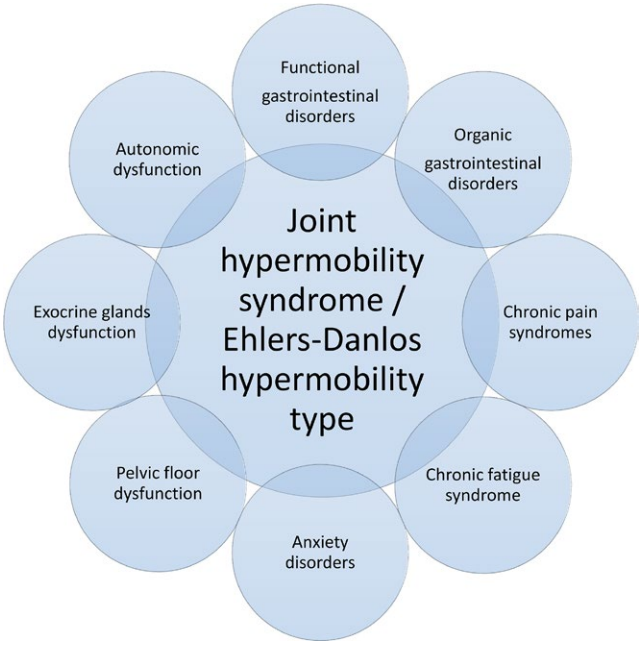

FIGURE 1 Systemic manifestations of joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. Adapted from Castori et al.[1]

Key Points

- Previous studies have shown a remarkable association between functional gastrointestinal (GI) disorders and joint hypermobility syndrome (JHS)/Ehlers-Danlos syndrome hypermobility type (EDS-HT), suggesting that about 50% of patients with functional dyspepsia and 40% of patients with irritable bowel syndrome have JHS/EDS-HT.
- Patients with functional GI disorders who meet the criteria for JHS/EDS-HT may therefore represent a distinct phenotype but is probably under-recognized by gastroenterologists.
- We here provide a summary of the literature and formulate a number of hypotheses to explain this commonly observed association. We also give a clinical recommendation to practicing gastroenterologist with regard to the management of symptoms in patients with JHS/EDS-HT.

EDS-HT and JHS: (i) EDS-HT and JHS are the same disorder in all circumstances; (ii) EDS-HT and JHS are partially overlapping conditions and correspond to the same disorder in selected circumstances (e.g., familial cases); and (iii) EDS-HT and JHS are two distinct disorders. Available literature however is scarce of data in support to any of the above hypotheses.[7] Because of this lack of evidence, we use the term JHS/EDS-HT throughout this review article.

A central defining feature of JHS/EDS-HT is generalized joint hypermobility (gJHM), which refers to the characteristic of being able to actively and/or passively move joints beyond normal limits.[9] Joint hypermobility can affect a few joints (localized or monoarticular joint hypermobility) or several joints in multiple body sites (gJHM). Generalized joint hypermobility, in the absence of other symptoms, is considered to be a harmless trait and may even confer advantages for certain areas of endeavor such as ballet dancers and gymnasts.[10] In Western populations, the prevalence of gJHM is in the order of 10-20%, and even higher rates have been described in Asian and African population groups.[11,12] The reported population prevalence of JHS/EDS-HT of 1:5000 suggests that the risk of developing the syndrome in an individual with gJHM is small.[13]

Generalized joint hypermobility can be screened for using a simple validated five-point questionnaire, but is formally evaluated using the Beighton score (see Table 1). The definitive diagnosis of JHS/EDS-HT however requires additional criteria to be fulfilled. Whereas the Villefranche criteria (1997, Table 2) are traditionally used for the diagnosis of EDS-HT, JHS is diagnosed using the Brighton criteria (1998, Table 2).[14,15] The reader can appreciate the considerable overlap between the two different diagnostic criteria. International consensus currently considers the Brighton criteria as an extension of the Villefranche criteria and is therefore more often applied in clinical practice.[1] In addition, the Brighton criteria are more suitable for assessing adults considering the natural loss of joint mobility by age, whereas the Villefranche criteria are more adequate for evaluating children and young adults.[9] However, more recently, the diagnostic criteria are being harmonized by a group of international experts and the new criteria are expected to be published toward the end of 2016.

Interestingly, JHS/EDS-HT has specifically been shown to be highly prevalent in patients with functional GI disorders (FGIDs),[3–5,16,17] which include irritable bowel syndrome (IBS) and functional dyspepsia (FD). Functional GI disorders are common, affecting up to 20% of the general population and accounting for more than one-third of gastroenterologists' workload in secondary care.[18] Although the severity of complaints varies, it has been demonstrated that FGIDs exert a marked socioeconomic burden through increased absenteeism and healthcare utilization.[19] An important aspect is the chronic character of complaints and significant comorbidities associated with FGID, for example, fibromyalgia, autonomic dysfunction, and psychopathology, which can have profound effects on quality of life in these patients.[20] It is tempting to assume that patients presenting with signs and symptoms representative of JHS/EDS-HT constitute a separate clinical subgroup of patients with FGIDs in whom therapeutic considerations may differ from those without JHS/EDS-HT. The aim of this review was to examine the nature of GI symptoms and their underlying pathophysiology in JHS/EDS-HT with a particular focus on the functional GI disorders encountered in these patients and to consider the clinical implications of the diagnosis for practicing clinicians.

2 | METHODS

Evidence to support this review was obtained from an electronic database search via PubMed using the following search Medical Subject

TABLE 1 Assessment of generalized joint hypermobility

Five-point questionnaire for generalized joint hypermobility (screening tool)
Answering yes to two or more of these questions suggests hypermobility with sensitivity of 85% and specificity of 90%
1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your kneecap or shoulder dislocate on more than one occasion?
5. Do you consider yourself "double-jointed"?
Beighton score (clinical assessment of joint hypermobility). Score 0-9.
1. Passive dorsiflexion of the little fingers beyond 90 degrees (one point for each hand). Two points
2. Passive apposition of the thumbs to the flexor aspects of the forearms (one point for each thumb). Two points
3. Hyperextension of the elbows beyond 10 degrees (one point for each elbow). Two points.
4. Hyperextension of the knees beyond 10 degrees (one point for each knee). Two points.
5. Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor. One point.

TABLE 2 Diagnostic criteria for joint hypermobility syndrome (JHS, left) and Ehlers-Danlos syndrome hypermobility type (EDS-HT, right)

1998 Brighton Classification for JHS [14]	Villefranche criteria for the EDS-HT [15]
Major criteria	Major criteria
1. Beighton score of 4/9 or greater (either currently or historically) 2. Arthralgia for longer than 3 months in four or more joints	1. Generalized joint hypermobility (defined as Beighton score ≥5/9) 2. Skin involvement: hyperextensibility or smooth velvety skin
Minor criteria	Minor criteria
1. Beighton score of 1, 2, or 3/9 (0, 1, 2, or 3 if aged 50þ) 2. Arthralgia (for 3 months or longer) in 1-3 joints, back pain (for 3 months or longer), or spondylosis, spondylolysis, spondylolisthesis 3. Dislocation/subluxation in more than one joint or in one joint on more than one occasion 4. Soft tissue rheumatism: three or more lesions (e.g., epicondylitis, tenosynovitis, bursitis) 5. Marfanoid habitus (tall, slim, span/height ratio >1.03 upper:lower segment ratio <0.89, arachnodactyly [positive Steinberg/wrist signs]) 6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring 7. Eye signs: drooping eyelids, myopia, or antimongoloid slant 8. Varicose veins, hernia, or uterine/rectal prolapse	1. Recurrent joint dislocations 2. Chronic limb/joint pain 3. Positive family history
A diagnosis of JHS requires two major criteria, or one major and two minor, or four minor, or two minor in the presence of an unequivocally affected first-degree relative.	*The presence of at least one major and one minor criteria is indicative, and a definitive diagnosis of EDS-HT requires at least two major criteria*

Headings terms: Ehlers-Danlos hypermobility type or Ehlers-Danlos type III or JHS and GI manifestations or GI symptoms or functional GI disorders. This search strategy yielded 83 articles. Articles discussing gJHM, thereby focusing on the trait rather than the syndrome, were excluded from further analysis. Although these may also include patients with JHS/EDS-HT, this population was considered too heterogeneous, which could complicate the generalizability of results. For the same reason, articles discussing different EDS subtypes than JHS/EDS-HT were excluded. Furthermore, case reports were excluded from analysis because we believe these might not give an appropriate representation of the JHS/EDS-HT population and only describe the most catastrophic phenotypes. We would, however, like to refer the reader to a recent review summarizing these papers.[21] All residual articles discussing GI manifestations in JHS/EDS-HT or JHS were further examined for useful references that did not emerge in the initial search. A total of 11 articles that focussed on GI manifestations in JHS/EDS-HT were selected for inclusion. One study found a high prevalence of gJHM in a pediatric population of patients with FGIDs; however, as it did not meet the inclusion criteria for the current manuscript, we have not provided further details.[22] Unfortunately, no studies discussing GI manifestations in pediatric JHS/EDS-HT patients were identified, limiting evidence of the current review to the adult population. In addition to the systematic search on the GI manifestations in JHS/EDS-HT as described above, we investigated current

literature to explore non-GI manifestations in JHS/EDS-HT in a narrative approach to merge parallel findings in order to offer a reasonable insight into pathogenesis.

3 | RESULTS

3.1 | JHS/EDS-HT and functional GI disorders

Several reports have been published to describe the putative relationship between JHS/EDS-HT and GI symptoms (see Table S1).[3–5,16,17]

In 2010, Castori et al. published a pilot study on manifestations of JHS/EDS-HT in 21 patients, in which GI symptoms were present in 86% (18/21) of patients, including dyspepsia (66.7%), gastro-esophageal reflux (57.1%), recurrent abdominal pain (61.9%), and constipation/diarrhea (33.3%).[3]

Fikree et al. were the first to perform a prospective evaluation to investigate the relationship between JHS/EDS-HT and FGIDs. The prevalence of JHS/EDS-HT was found to be 33% in an unselected group of patients referred to their secondary care gastroenterology clinic.[16] In addition, these patients were compared to patients who were referred from the rheumatology clinic with a previously confirmed diagnosis of JHS/EDS-HT and were characterized by higher prevalence of various musculoskeletal features and higher Beighton scores. A high prevalence of GI symptoms was found in all groups, although symptoms were most common in rheumatology referrals (see Table 3). Moreover, these patients were more likely to be diagnosed with a FGID (see Figure 2).

More recently, Fikree et al. prospectively examined the relationship between JHS/EDS-HT and FGIDs in a case–control design study comparing patients with a diagnosis of a FGID or an organic GI disorder.[17] There was a significantly higher prevalence of JHS/EDS-HT in the FGID group (39% versus 27.5%, P=.002). Interestingly, the prevalence of JHS/EDS-HT was 51% in patients with postprandial distress syndrome, a subtype of FD.

In 2013, Zeitoun et al. performed a cohort study of patients with EDS and found that gastro-esophageal reflux (heartburn and regurgitation) and dyspepsia (epigastric pain, nausea, postprandial fullness, and belching) were present in around 70% of the subjects.[5] Furthermore, 48% of all participants met criteria for IBS (using the Rome III criteria) and 36% had functional constipation. In addition, these authors reported a greatly reduced GI-related quality-of-life index.

More recently, Nelson et al. performed a retrospective review of patients diagnosed with EDS, of which 71% had JHS/EDS-HT.[4] Of 687 patients, 378 (55%) had GI symptoms, most notably abdominal pain (56%), nausea (44%), constipation (42%), heartburn (38%), irritable

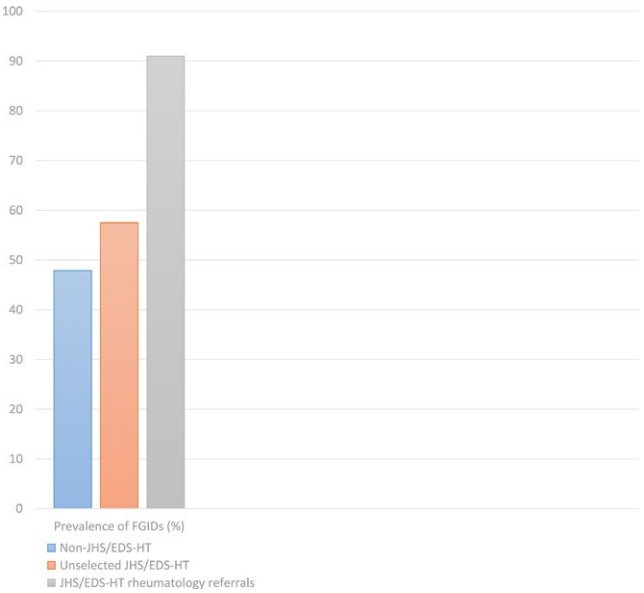

FIGURE 2 Prevalence of functional gastrointestinal disorders in non-JHS/EDS-HT patients, patients with JHS/EDS-HT from the unselected group, and patients with JHS/EDS-HT referred from rheumatology

TABLE 3 Comparison of prevalence of GI symptoms in non-JHS/EDS-HT patients, patients with JHS/EDS-HT from the unselected group, and patients with JHS/EDS-HT referred from rheumatology

	Non-JHS/EDS-HT (CI)	JHS/EDS-HT Unselected (CI)	OR adjusted (CI)	JHS/EDS-HT Rheumatology (CI)	OR adjusted for age and gender (CI)
Alternating bowel habit	30.4 (25.6-35.6)	38.6 (31.2-46.3)	1.38 (0.96-2.03)	65.8 (49.4-79.9)	1.70 (1.27-2.27)
Abdominal pain	83.2 (76.9-85.4)	90.3 (83.2-93.4)	1.62 (0.91-2.9)	100 (91.4-100)	2.04 (1.20-3.45)
Globus	19.1 (15.1-23.6)	27.2 (20.7-34.4)	1.46 (0.94-2.26)	47.7 (32.5-63.3)	1.64 (1.21-2.22)
Heartburn	23.5 (19.2-28.3)	33.0 (26.1-40.4)	1.66 (1.1-2.5)	25.0 (13.2-40.3)	1.29 (0.96-1.75)
Water brash	18.5 (14.5-22.9)	30.9 (24.1-38.3)	2.02 (1.3-3.1)	29.5 (16.8-45.2)	1.59 (1.17-2.16)
Dysphagia	10.6 (7.5-14.3)	1647.1 (11.0-22.4)	1.59 (0.92-2.7)	31.8 (18.6-47.6)	1.79 (1.25-2.56)
Early satiety	42.8 (37.7-48.0)	53.4 (45.7-61.0)	1.4 (0.98-2.1)	79.1 (64.0-90.0)	1.68 (1.26-2.23)
Postprandial fullness	27.1 (22.6-32.1)	41.4 (34.0-49.1)	1.74 (1.2-2.6)	61.4 (45.5-75.6)	1.72 (1.29-2.29)
Regurgitation	11.4 (8.3-15.2)	17.5 (12.2-24.1)	1.57 (0.93-2.6)	33.3 (19.6-49.5)	1.70 (1.20-2.42)
Bloating	47.9 (42.6-53.2)	54.3 (46.6-61.8)	1.15 (0.79-1.67)	88.6 (75.4-96.2)	1.60 (1.20-2.14)

Reprinted from A prospective evaluation of undiagnosed joint hypermobility syndrome in patients with gastrointestinal symptoms. CIs for proportions and ORs are presented in parentheses.
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bowel-like symptoms (30%), vomiting (25%), and diarrhea (23%). In patients with EDS who underwent physiology testing, abnormal gastric emptying was observed in 22.3%; 11.8% delayed and 10.5% accelerated. Colonic transit was abnormal in 28.3%; 19.6% delayed and 8.7% accelerated. A rectal evacuation disorder was confirmed in 18 of 30 (60%) patients who underwent anorectal physiology measurements. The finding of GI dysmotility in these patients is consistent with a previously observed high prevalence of dysmotility in patients with gJHM attending tertiary care neurogastroenterology clinics.[23]

Table 4 shows a summary of prevalence data on GI symptoms in JHS/EDS-HT from the currently published studies.

3.2 | JHS/EDS-HT and organic disorders

3.2.1 | Hiatus hernia

Zeitoun et al. reported that 19 of 72 patients with EDS (26.4%) that had undergone upper endoscopy were shown to have a hiatal hernia.[6] This corresponds to the number reported by Al-Rawi et al. investigating the presence of hiatal hernias in patients with gJHM (22%).[24]

3.2.2 | Pelvic organ prolapse and defecatory disorders

Pelvic organ prolapse has been extensively investigated in the past, though mainly in gJHM.[25] One small study found a high prevalence (75%) of pelvic organ prolapse in women with EDS.[2] Another study demonstrated the frequent occurrence of defecatory problems in patients with JHS/EDS-HT, most notably straining (61.7%), incomplete evacuation (63%), and digitation (33.3%).[26] Furthermore, the majority (73.3%) of the JHS/EDS-HT group had a clinically significant prolapse compared with 35% of the control group (P<.001).

In an earlier study, Manning et al. investigated the association between obstructive defecation and lower urinary tract dysfunction in JHS/EDS-HT.[27] It was demonstrated that women presenting with lower urinary tract dysfunction also frequently had symptoms of obstructed defecation. Furthermore, patients with obstructed defecation were more likely to show symptoms of JHS/EDS-HT (70.6% vs 50.0%, P<.001). JHS/EDS-HT was therefore considered an important factor in the above-mentioned association.

TABLE 4 Gastrointestinal symptoms in patients with JHS/EDS-HT (Collective data from all studies included for analysis)

Symptom	Range	Median (IQR)	References
Nausea	32-71%	45 (35-65)	(4,5,16)
Vomiting	14-25%	14	(4,16)
Globus	(1%[a]) 27-48%	27	(4,16)
Heartburn	25-69%	38 (29-63%)	(3–5,16)
Regurgitation	(4%[a]) 18-69%	33 (8-60%)	(3–5,16)
Water brash	(1%[a]) 30-31%	30	(4,16)
Belching	(3%[a]) 41-71%	43 (13-65%)	(4,5,16)
Bloating	(17%[a]) 54-89%	54	(4,16)
Dysphagia	11-63%	24 (13-55%)	(4,5,16)
Dyspepsia	(11%[a]) 34-63%	43 (17-63%)	(3,4,16)
Epigastric pain	79%		(5)
Postprandial fullness	(7%[a]) 41-67%	51 (16-66%)	(4,5,16)
Abdominal pain	56-100%	76 (58-98%)	(3,4,16)
IBS-like symptoms	30-47%	39	(4,5)
Constipation	19-42%	35 (23-41%)	(3–5,16)
Diarrhea	23-42%	32 (25-40%)	(3–5,16)
Alternating bowel habit	39-66%	52	(16)

IQR: interquartile range, given when available.

[a]Globus, regurgitation, water brash, belching, bloating, dyspepsia, and postprandial fullness were less prevalent in the study of Nelson et al. (values shown in parentheses).

3.2.3 | Inflammatory bowel disease

Fikree et al. demonstrated a relatively high prevalence of JHS/EDS-HT in patients with Crohn's disease (8/25, 32%), but not in patients with ulcerative colitis (8/38, 21%).[17] An earlier study found a significantly higher prevalence of gJHM in patients with Crohn's disease (70.7%) compared to patients with ulcerative colitis (35.7%) (P=.0063) and healthy controls (25.3%) (P<.0001). No differences were found in the proportion of gJHM between patients with UC and healthy controls (P=.3). The prevalence of JHS/EDS-HT was relatively low in both groups although it was higher in patients with Crohn's disease than in patients with UC (12.2% Crohn's disease, 3.57% UC).[28]

3.2.4 | Celiac disease

One small study demonstrated that the prevalence of celiac disease was 16% in the JHS/EDS-HT group, which is significantly higher than the estimated population prevalence (1%).[29] These results were broadly corroborated in another prospective case-controlled study where JHS/EDS-HT was found in four of 13 (31%) patients attending GI clinics with a new diagnosis of celiac disease.[17] More recently, Laszkowska et al. performed a nationwide population-based cohort study in Sweden, reporting a 49% increased risk of JHS/EDS-HT in patients with celiac disease (95% CI = 1.07-2.07; P=.018).[30]

Table S2 shows a summary of prevalence data on organic GI disorders in JHS/EDS-HT from the currently published studies. It is important to note that the majority of studies performed in patients with JHS/EDS-HT to assess GI symptoms or abnormalities (either functional or organic) have a number of limitations. The patient populations investigated are generally highly selected as these comprise patients attending secondary/tertiary care clinics. We already mentioned the impact of higher Beighton scores on GI symptoms. These studies may have therefore included more severe cases of JHS/EDS-HT. Furthermore, several of the studies are based on a small number of patients. Thus, these findings are not necessarily generalizable to the majority of patients with JHS/EDS-HT, most of whom remain undiagnosed and in the community. Primary care studies investigating GI symptoms in JHS/EDS-HT are currently scarce. Fikree et al. demonstrated that

healthy students who met criteria for JHS/EDS-HT were more likely to experience multiple GI symptoms in particular postprandial distress syndrome, as compared to healthy non-JHS/EDS-HT students.[31] Finally, comparison of different studies is troublesome due to large differences in methodology (i.e., diagnostic criteria used, healthcare setting, and study design). We were therefore unable to perform a meta-analysis of data.

3.3 | Relevant non-GI manifestation in JHS/EDS-HT

There is growing evidence that patients with JHS/EDS-HT have an increased prevalence of chronic pain syndromes, autonomic dysfunction, and psychopathology. Because these factors are also comorbid with functional GI disorders,[32,33] the evidence for their involvement with JHS/EDS-HT will be described below.

3.3.1 | Chronic widespread pain and opiate use

A large survey conducted in the Netherlands among patients with EDS (including 157 with hypermobility subtype) showed that 98% of patients experienced chronic, mostly musculoskeletal pain.[34] Pain severity changed over time but remained continuously present in 85% of patients. It has recently been postulated that chronic widespread pain in JHS/EDS-HT is due to the persistent nociceptive input as a result of joint abnormalities that triggers central sensitization in the dorsal horn neurons.[35] Moreover, such central sensitization may also be the cause of generalized hyperalgesia, which has been demonstrated in both children and adults with JHS/EDS-HT.[36] It should be noted however that other factors than musculoskeletal pain may contribute to chronic pain in patients with JHS/EDS-HT. For example, a high prevalence of small fiber neuropathy has been reported in patients with JHS/EDS-HT, resulting in neuropathic pain.[37]

In the Dutch survey mentioned above, 89% of the patients with EDS who had pain were on one or more analgesics with 23% being on tramadol. Fikree et al. found similar numbers of opioid use in patients with JHS/EDS-HT referred by the rheumatologist (29.6%).[16] Opioid use is particularly relevant in these patients because of their potential to exacerbate GI symptoms and result in opioid induced bowel dysfunction and potentially narcotic bowel syndrome, which makes management even more challenging.[38,39]

3.3.2 | Autonomic dysfunction

Patients with joint hypermobility syndrome/EDS-HT can experience symptoms suggestive of (pre)syncope (i.e., light-headedness, dizziness, and actual fainting), and palpitations and chest pain. Hakim and Grahame reported symptoms of presyncope in 41% of patients with JHS/EDS-HT, compared with only 15% in the control group.[40] A subset of these symptoms may be explained by the association of JHS/EDS-HT with postural tachycardia syndrome (PoTS). Postural tachycardia syndrome is defined as an elevation of the heart rate of at least 30 bpm within 10 min after standing upright, or a heart rate >120 bpm after standing. The prevalence of PoTS in patients with JHS/EDS-HT reached 15% in one study.[41] Autonomic dysfunction, such as PoTS, orthostatic hypotension, and/or uncategorized orthostatic intolerance are seen in three of four patients with JHS/EDS-HT.[42] Postural tachycardia syndrome can be treated with a combination of non-pharmacological approaches, a structured exercise training program, and often some pharmacological support. Several hypotheses have been formulated to explain why orthostatic intolerance is so strongly associated with JHS/EDS-HT. These include among others, altered vascular tissue elasticity, impaired peripheral vasoregulation, physical deconditioning, and neuropathies.[40,43,44]

Postural tachycardia syndrome, independent of EDS status, is associated with GI symptoms and with dysmotility of the stomach, small bowel, and colon, as demonstrated by a number of previous studies.[45–47] Patients with GI symptoms who meet the criteria for JHS/EDS-HT have significantly higher autonomic scores for orthostatic domains ($P<.001$) compared to patients without JHS/EDS-HT.[16]

3.3.3 | Psychiatric comorbidity

Since the late 80s, anxiety disorder has been described to appear more commonly in individuals with gJHM.[48] More recently, these associations have also been found in patients with JHS/EDS-HT, as extensively reviewed by Sinibaldi et al.[49] Furthermore, panic disorder, agoraphobia, simple phobia, and dysthymic disorder or major depression were all found to have a strong association with JHS/EDS-HT.[50] A 15-year follow-up cohort study of patients with JHS/EDS-HT showed a cumulative incidence of panic disorder of 41.4% in the JHS/EDS-HT group, compared with only 1.9% in the non-JHS/EDS-HT control group.[51]

The observed prevalence of anxiety and other psychiatric comorbidities is higher in JHS/EDS-HT than other chronic pain conditions, but the basis for this is not fully understood.[52] Several studies have hypothesized this to be related to increased interoception, which refers to the concept of sensory bodily information that is continuously assessed and interpreted in relation to certain expectations, which results in a person becoming aware of his/her autonomic bodily state. This interoceptive sensitivity enhances the salience of previously innocuous stimuli, meaning that bodily prediction error signals (e.g., increased heart rate) are attributed to ambiguous environmental stimuli, which in turn become potential threats.[53] Interoceptive sensitivity can be associated with enhanced emotional responsiveness resulting in anxiety and hypervigilance.[54] It has been confirmed through questionnaires that people with gJHM score higher on a body awareness index,[55] a factor which can contribute to the development of anxiety.

Other possible hypotheses put forward to explain the increased psychiatric manifestations in JHS/EDS-HT include the fact that a greater perception of joint instability and the frequency with which this impacts on activities of daily living can contribute to anxiety.[52] Furthermore, frequent falling due to autonomic dysfunction can sometimes result in kinesiophobia (fear of movement)—an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury.[56]

In addition, a considerable phenomenological overlap exists between symptoms of both PoTS and anxiety (i.e., panic, dizziness, palpitations) and it is possible that these symptoms of orthostatic intolerance may exacerbate anxiety, particularly so when combined with enhanced interoception.

A recent study demonstrated a significant association of abdominal, joint, and neuropathic pain with having a psychiatric disorder in EDS.[57] However, other GI manifestations, notably symptoms of dyspepsia and reflux, were not significantly affected by the presence of psychopathology.[16] This would suggest that the contribution of psychopathology to GI manifestations in JHS/EDS-HT may be symptom dependent and primarily related to pain.

4 | DISCUSSION

Scientific evidence suggests an association between JHS/EDS-HT and GI disorders, and these patients meet the criteria for FGIDs, specifically those with upper GI symptoms.[4,5,16,17] Interestingly, postprandial distress syndrome, a subtype of dyspepsia, showed the strongest association with JHS/EDS-HT in one study,[17] and symptoms of this disorder including bloating and postprandial fullness were consistently associated with JHS/EDS-HT in multiple studies (see Table 4), but the etiology behind this remains to be elucidated. Another important observation is that patients with JHS/EDS-HT with lower Beighton scores and modest musculoskeletal involvement seem to experience fewer GI symptoms.[16] It could be speculated that these patients would have a better prognosis concerning GI symptoms compared with their more hypermobile peers, although this hypothesis will need to be assessed in future studies.

The prerequisite step to the development of a more complete understanding of the relationship between JHS/EDS-HT and GI symptoms is the objective assessment as to whether such symptoms are attributable to any demonstrable physiological or anatomical abnormalities therein. It should be noted that, to date, only a preliminary study has examined this specifically. In this study, esophageal motility was evaluated in 17 JHS/EDS-HT with dysphagia symptoms. This study, as of yet available in abstract form, has shown that 59% (10/17) of patients had evidence of esophageal dysmotility.[58] No other studies have specifically examined the physiological and anatomical basis of GI symptoms in JHS/EDS-HT. Although several studies described the findings of physiological investigations in JHS/EDS-HT, including Nelson et al.,[4] as discussed in detail above, it is difficult to interpret these in the absence of a clinical background of the patients. It therefore remains challenging to ascertain the pathophysiology of GI symptoms and FGIDs seen in patients with JHS/EDS-HT. We here formulate a number of hypotheses on pathogenesis, including ones related to abnormal motility, altered biomechanical properties (e.g., compliance), increased sensitivity, and changes in the brain–gut axis, which will be discussed in more detail below.

It is tempting to assume that GI symptoms in patients with JHS/EDS-HT would relate to altered motility and biomechanics of the GI tract as a result of the connective tissue anomaly. It is possible that variations in connective tissue and, in particular, in the extracellular matrix (ECM) composition in JHS/EDS-HT are responsible for laxity of joints, pelvic floor, and other sites including the GI tract, most notably the intestinal wall. A previous study in gJHM found evidence for significant anorectal anatomical abnormalities, including rectoceles[25]—no such studies have yet been performed in JHS/EDS-HT. To date, no collagen defects and/or associated mutations have been found in JHS/EDS-HT. Only in 5-10% of patients a mutation in TNXB, the gene that codes for tenascin-X, a glycoprotein in the ECM that is responsible for organization and maintenance of the matrix itself, was linked to an autosomal recessive form of JHS/EDS-HT.[59,60] Notably, we have previously reported that GI symptoms are encountered frequently in tenascin-X-deficient patients.[61] For the remainder of patients, JHS/EDS-HT is a diagnosis of exclusion.

Interestingly, investigations aimed at assessing GI motor function, such as reported by Nelson et al., have demonstrated both increased *and* delayed gastric emptying and colonic transit, which would suggest involvement of other mechanisms than merely alterations in the mechano-elastic properties of the intestinal wall. Moreover, very recently, animal studies demonstrated that changes in mechano-elastic properties of the intestine result in altered mechano-sensory afferent responses.[62] Indeed, considerable scientific evidence exists to support a role for the ECM in nerve function. Neurons express certain receptors that enable them to interact with the surrounding connective tissue. Furthermore, the ECM can affect maturation and function of synapses in the peripheral and central nervous system (for review, see Ref. 63). More specifically, *in vitro* studies have demonstrated that the ECM microenvironment has profound influence on the differentiation of neuronal subtypes innervating smooth muscle cells of the intestine.[64] In fact, the composition of the ECM was able to influence cholinergic and nitrergic neurotransmission in these neural cells and their responses to electrical field stimulation. This suggests significant effects of the ECM on the neurodevelopment of the enteric nervous system. It remains to be established, however, whether such neurodevelopmental changes are present in patients with JHS/EDS-HT and whether this indeed has an effect on the development of GI abnormalities and symptoms through influencing afferent signaling.

We hypothesize that presumed changes in afferent signaling may result in (i) increased peripheral discharge of nociceptive information (peripheral sensitization) or (ii) augmentation of afferent information at the level of spinal dorsal horn neurones (central sensitization). Sensitization refers to a reduction in the threshold for perception of sensory stimuli arising from visceral organs. A commonly accepted hypothesis in the development of functional GI disorders is indeed related to visceral hypersensitivity.[65] We therefore speculate that neurodevelopmental changes as a result of ECM abnormalities in JHS/EDS-HT may render intestinal afferents more prone to sensitization. However, no studies have specifically examined the presence of visceral hypersensitivity in JHS/EDS-HT, let alone to establish whether this is related to alterations in afferent signaling.

In summary, although an association between GI symptoms and JHS/EDS-HT appears to have been consistently reported, it remains to be established what the exact nature of the connective tissue anomaly

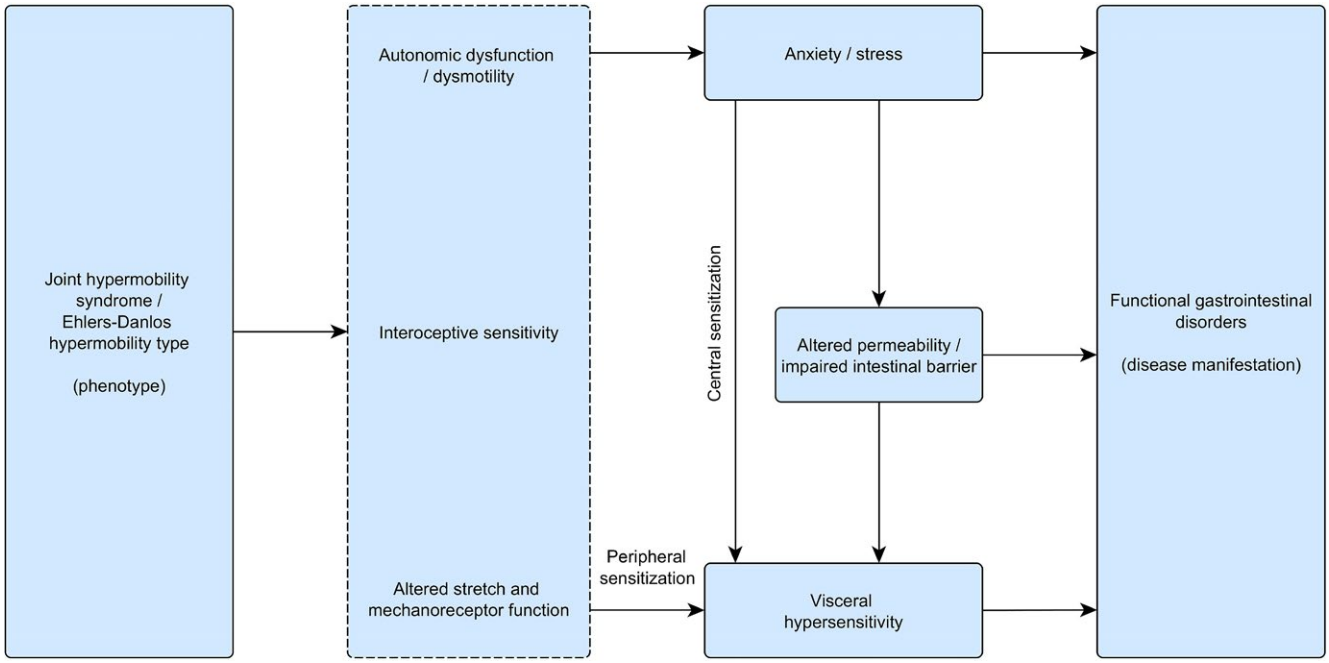

FIGURE 3 Diagram illustrating possible pathways for the pathogenesis of functional gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type

is in relation to GI function and symptom generation. Although several hypotheses have been formulated (see Figure 3 for schematic overview), the scarcity of data warrants further mechanistic studies to identify the pathophysiological basis of this association. We believe that systematic evaluation of GI sensorimotor function and genotypical characterization of patients with overlap between JHS/EDS-HT and FGIDs is an important research area in the future.

5 | CONCLUSIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

We here provide recommendation for the clinical management of patients with JHS/EDS-HT presenting with GI symptoms, which are based on expert opinion rather than scientific evidence due to the current paucity of data.

1. *Recognition*. It is important for gastroenterologists to consider the diagnosis of JHS/EDS-HT in patients with FGIDs and multiple musculoskeletal symptoms. When JHS/EDS-HT is suspected, the patient should be referred to a specialist that is familiar with the disorder (i.e., clinical geneticist or rheumatologist) in order to establish a definitive diagnosis.
2. *Multidisciplinary approach*. Recognition of comorbidities as part of a multisystem disorder warranting a multidisciplinary approach is an important clinical imperative. Pointing out to patients that the comorbidities of JHS/EDS-HT, including its GI manifestations, are the result of a multisystem disorder, may aid patients' psychological health by providing reassurance and a potential explanation of their symptoms.
3. *Opioid use*. An attempt should be made to decrease the use of opioids and to consider replacing them with pain modulators (such as tricyclic antidepressant, gabapentinoids, or serotonin–norepinephrine reuptake inhibitors) instead. The efficacy of pain modulators in this group of patients of course requires further study.
4. *Nutritional aspects*. Attention should be given to maintain an optimal nutritional status and prevent the development of nutritional deficiencies. A number of potentially beneficial dietary supplements have been reported for the classical subtypes of EDS, including carnitine, co-enzyme Q10, high doses of vitamin C (1500 mg/day), and various chondral protectors.[66] The exact role for these supplements in the therapy for JHS/EDS-HT remains to be further elucidated.

Studies have shown a remarkable association between FGIDs and JHS/EDS-HT, suggesting that about 50% of patients with FD and 40% of patients with IBS have JHS/EDS-HT. This observation may indeed represent the first step toward the identification of a new pathophysiological basis for a substantial subgroup of patients with FGID. The discovery of an association of a disorder of connective tissue with hitherto unexplained GI symptoms has raised the prospect of identification of important therapeutic targets in the signaling and interaction between ECM and intestinal neural cells. It is of interest that despite extensive advances in our understanding of gut sensorimotor function, the aspect that is least studied is the role of connective tissue in gut function. Not very long ago—against all odds—Helicobacter pylori was found to be the cause for peptic ulcer disease. Time will tell whether the putative association between JHS/EDS-HT and FGIDs has a similar potential within neurogastroenterology.

DISCLOSURE

No competing interests declared.

AUTHOR CONTRIBUTION

BB, DK, and AF wrote the manuscript; LV and AM provided important intellectual content; ADF and QA critically reviewed manuscript; QA had overall responsibility for this paper and conceptual guidance.

REFERENCES

1. Castori M. Ehlers-danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. *ISRN Dermatol*. 2012;2012:751768.
2. Carley ME, Schaffer J. Urinary incontinence and pelvic organ prolapse in women with Marfan or Ehlers Danlos syndrome. *Am J Obstet Gynecol*. 2000;182:1021–1023.
3. 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:556–564.
4. Nelson AD, Mouchli MA, Valentin N, et al. Ehlers Danlos syndrome and gastrointestinal manifestations: a 20-year experience at Mayo Clinic. *Neurogastroenterol Motil*. 2015;27:1657–1666.
5. Zeitoun JD, Lefevre JH, de Parades V, et al. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: results of a national cohort study on 134 patients. *PLoS ONE*. 2013;8:e80321.
6. De Wandele I, Rombaut L, Malfait F, De Backer T, De Paepe A, Calders P. Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos syndrome. *Res Dev Disabil*. 2013;34:873–881.
7. Castori M, Colombi M. Generalized joint hypermobility, joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet Part C Semin Med Genet*. 2015;169C:1–5.
8. Hakim AJ, Keer R, Grahame R. What is the joint hypermobility syndrome? JHS from the cradle to the grave. In: Grahame R, ed. *Hypermobilty, Fibromyalgia and Chronic Pain*. London: Churchill Livingstone; 2010:19–33.
9. Colombi M, Dordoni C, Chiarelli N, Ritelli M. Differential diagnosis and diagnostic flow chart of joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type compared to other heritable connective tissue disorders. *Am J Med Genet Part C Semin Med Genet*. 2015;169C:6–22.
10. Steinberg N, Hershkovitz I, Zeev A, Rothschild B, Siev-Ner I. Joint hypermobility and joint range of motion in young dancers. *J Clin Rheumatol*. 2016;22:171–178.
11. Hakim AJ, Cherkas LF, Grahame R, Spector TD, MacGregor AJ. The genetic epidemiology of joint hypermobility: a population study of female twins. *Arthritis Rheum*. 2004;50:2640–2644.
12. Farmer AD, Douthwaite H, Gardiner S, Aziz Q, Grahame R. A novel in vivo skin extensibility test for joint hypermobility. *J Rheumatol*. 2010;37:1513–1518.
13. Levy HP. Ehlers-Danlos syndrome, hypermobility type. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, eds. *GeneReviews*. Seattle: University of Washington; 1993–2016: 1–19.
14. Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol*. 2000;27:1777–1779.
15. 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;77:31–37.
16. Fikree A, Grahame R, Aktar R, et al. A prospective evaluation of undiagnosed joint hypermobility syndrome in patients with gastrointestinal symptoms. *Clin Gastroenterol Hepatol*. 2014;12:1680–1687 e1682.
17. 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;27:569–579.
18. Shivaji UN, Ford AC. Prevalence of functional gastrointestinal disorders among consecutive new patient referrals to a gastroenterology clinic. *Frontline Gastroenterol*. 2014;5:266–271.
19. Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil*. 2008;20(Suppl 1):121–129.
20. Riedl A, Schmidtmann M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res*. 2008;64:573–582.
21. Castori M, Morlino S, Pascolini G, Blundo C, Grammatico P. Gastrointestinal and nutritional issues in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet Part C Semin Med Genet*. 2015;169C:54–75.
22. Kovacic K, Chelimsky TC, Sood MR, Simpson P, Nugent M, Chelimsky G. Joint hypermobility: a common association with complex functional gastrointestinal disorders. *J Pediatr*. 2014;165:973–978.
23. Zarate N, Farmer AD, Grahame R, et al. Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? *Neurogastroenterol Motil*. 2010;22:252–e278.
24. Al-Rawi ZS, Al-Dubaikel KY, Al-Sikafi H. Joint mobility in people with hiatus hernia. *Rheumatology*. 2004;43:574–576.
25. Mohammed SD, Lunniss PJ, Zarate N, et al. Joint hypermobility and rectal evacuatory dysfunction: an etiological link in abnormal connective tissue? *Neurogastroenterol Motil*. 2010;22:1085–e1283.
26. Mastoroudes H, Giarenis I, Cardozo L, et al. Prolapse and sexual function in women with benign joint hypermobility syndrome. *BJOG*. 2013;120:187–192.
27. Manning J, Korda A, Benness C, Solomon M. The association of obstructive defecation, lower urinary tract dysfunction and the benign joint hypermobility syndrome: a case-control study. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;14:128–132.
28. Vounotrypidis P, Efremidou E, Zezos P, et al. Prevalence of joint hypermobility and patterns of articular manifestations in patients with inflammatory bowel disease. *Gastroenterol Res Pract*. 2009;2009:924138.
29. Danese C, Castori M, Celletti C, et al. Screening for celiac disease in the joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Am J Med Genet A*. 2011;155A:2314–2316.
30. Laszkowska M, Roy A, Lebwohl B, Green PH, Sundelin HE, Ludvigsson JF. Nationwide population-based cohort study of celiac disease and risk of Ehlers-Danlos syndrome and joint hypermobility syndrome. *Dig Liver Dis*. 2016;48:1030–1034.
31. Fikree A, Aktar R, Morris JK, Grahame R, Knowles CH, Aziz Q. The association between Ehlers-Danlos syndrome-hypermobility type and gastrointestinal symptoms in university students: a cross-sectional study. *Neurogastroenterol Motil*. 2016;00:1–9.
32. Farmer AD, Aziz Q. Visceral pain hypersensitivity in functional gastrointestinal disorders. *Br Med Bull*. 2009;91:123–136.
33. Van Oudenhove L, Vandenberghe J, Vos R, Holvoet L, Tack J. Factors associated with co-morbid irritable bowel syndrome and chronic fatigue-like symptoms in functional dyspepsia. *Neurogastroenterol Motil*. 2011;23:524–e202.
34. 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;40:370–378.

35. 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;20:1319–1325.
36. 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)*. 2016;1–22.
37. Cazzato D, Castori M, Lombardi R, et al. Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. *Neurology*. 2016;87:155–159.
38. Drossman D, Szigethy E. The narcotic bowel syndrome: a recent update. *Am J Gastroenterol*. 2014;2:22–30.
39. Farmer AD, Ferdinand E, Aziz Q. Opioids and the gastrointestinal tract - a case of narcotic bowel syndrome and literature review. *J Neurogastroenterol Motil*. 2013;19:94–98.
40. Hakim AJ, Grahame R. Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? *Rheumatology (Oxford)*. 2004;43:1194–1195.
41. Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. *Am J Med*. 2003;115:33–40.
42. Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. Postural tachycardia syndrome–current experience and concepts. *Nat Rev Neurol*. 2012;8:22–34.
43. De Wandele I, Rombaut L, Leybaert L, et al. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum*. 2014;44:93–100.
44. Vincent A, Whipple MO, Low PA, Joyner M, Hoskin TL. Patients with fibromyalgia have significant autonomic symptoms but modest autonomic dysfunction. *PM R*. 2016;8:425–435.
45. Loavenbruck A, Iturrino J, Singer W, et al. Disturbances of gastrointestinal transit and autonomic functions in postural orthostatic tachycardia syndrome. *Neurogastroenterol Motil*. 2015;27:92–98.
46. Wang LB, Culbertson CJ, Deb A, Morgenshtern K, Huang H, Hohler AD. Gastrointestinal dysfunction in postural tachycardia syndrome. *J Neurol Sci*. 2015;359:193–196.
47. Huang RJ, Chun CL, Friday K, Triadafilopoulos G. Manometric abnormalities in the postural orthostatic tachycardia syndrome: a case series. *Dig Dis Sci*. 2013;58:3207–3211.
48. Bulbena A, Duro JC, Mateo A, Porta M, Vallejo J. Joint hypermobility syndrome and anxiety disorders. *Lancet*. 1988;2:694.
49. Sinibaldi L, Ursini G, Castori M. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: the link between connective tissue and psychological distress revised. *Am J Med Genet Part C Semin Med Genet*. 2015;169C:97–106.
50. Bulbena A, Duro JC, Porta M, et al. Anxiety disorders in the joint hypermobility syndrome. *Psychiatry Res*. 1993;46:59–68.
51. Bulbena A, Gago J, Pailhez G, Sperry L, Fullana MA, Vilarroya O. Joint hypermobility syndrome is a risk factor trait for anxiety disorders: a 15-year follow-up cohort study. *Gen Hosp Psychiatry*. 2011;33:363–370.
52. Smith TO, Easton V, Bacon H, et al. The relationship between benign joint hypermobility syndrome and psychological distress: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2014;53:114–122.
53. Critchley HD, Garfinkel SN. Interactions between visceral afferent signaling and stimulus processing. *Front Neurosci*. 2015;9:286.
54. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*. 2010;35:169–191.
55. Eccles JA, Iodice V, Dowell NG, et al. Joint hypermobility and autonomic hyperactivity: relevance to neurodevelopmental disorders. *J Neurol Neurosur Ps*. 2014;85:e3–e3.
56. 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.
57. Hershenfeld SA, Wasim S, McNiven V, et al. Psychiatric disorders in Ehlers-Danlos syndrome are frequent, diverse and strongly associated with pain. *Rheumatol Int*. 2016;36:341–348.
58. Fikree A, Aziz Q, Jafari J, Grahame R, Sifrim D. Dysphagia in patients with the joint hypermobility syndrome. *Gut*. 2011;60:A181–A181.
59. Petersen JW, Douglas JY. Tenascin-X, collagen, and Ehlers-Danlos syndrome: tenascin-X gene defects can protect against adverse cardiovascular events. *Med Hypotheses*. 2013;81:443–447.
60. Zweers MC, Kucharekova M, Schalkwijk J. Tenascin-X: a candidate gene for benign joint hypermobility syndrome and hypermobility type Ehlers-Danlos syndrome? *Ann Rheum Dis*. 2005;64:504–505.
61. Fikree A, Aktar R, Keszthelyi D, Aziz Q. Patients with tenascin-X deficient Ehlers-Danlos syndrome experience gastrointestinal symptoms and meet the criteria for functional gastrointestinal disorders (Abstract). *UEGW* 2015.
62. Yang J, Zhao J, Chen P, Nakaguchi T, Grundy D, Gregersen H. Interdependency between mechanical parameters and afferent nerve discharge in hypertrophic intestine of rats. *Am J Physiol Gastrointest Liver Physiol*. 2016;310:376–386.
63. Barros CS, Franco SJ, Muller U. Extracellular matrix: functions in the nervous system. *Cold Spring Harb Perspect Biol*. 2011;3:a005108.
64. Raghavan S, Bitar KN. The influence of extracellular matrix composition on the differentiation of neuronal subtypes in tissue engineered innervated intestinal smooth muscle sheets. *Biomaterials*. 2014;35:7429–7440.
65. Keszthelyi D, Troost FJ, Simren M, et al. Revisiting concepts of visceral nociception in irritable bowel syndrome. *Eur J Pain*. 2012;16:1444–1454.
66. Mantle D, Wilkins RM, Preedy V. A novel therapeutic strategy for Ehlers-Danlos syndrome based on nutritional supplements. *Med Hypotheses*. 2005;64:279–283.

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