Gastrointestinal symptoms and nutritional issues in patients with hypermobility disorders: assessment, diagnosis and management

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ABSTRACT
Patients diagnosed with hypermobile Ehlers-Danlos syndrome and hypermobile spectrum disorders are increasingly presenting to secondary and tertiary care centres with gastrointestinal (GI) symptoms and nutritional issues. Due to the absence of specific guidance, these patients are investigated, diagnosed and managed heterogeneously, resulting in a growing concern that they are at increased risk of iatrogenic harm. This review aims to collate the evidence for the causes of GI symptoms, nutritional issues and associated conditions as well as the burden of polypharmacy in this group of patients. We also describe evidence-based strategies for management, with an emphasis on reducing the risk of iatrogenic harm and improving multidisciplinary team care.

WHAT IS HYPERMOBILITY?
The nomenclature for joint hypermobility disorders (HD) has changed recurrently, but recognises hypermobile spectrum disorder (HSD) with less strict phenotypic features; hypermobile Ehlers-Danlos syndrome (hEDS) with stricter phenotypic criteria; and other subtypes including classical or vascular Ehlers-Danlos syndrome with a more severe structural presentation (1,2) (table 1). Currently patients with HSD and hEDS increasingly present to gastroenterologists, and these groups of patients are the focus of this review. We will use the generic label HD hereafter, since there is no evidence currently for a clinical distinction between the two for gastroenterology presentation and management, and there is variability as to specific labelling in studies. It is thought that HSD and hEDS are heritable collagen abnormalities with multisystem implications, but unlike classical/vascular EDS, no genetic basis has yet been convincingly demonstrated.3 HSD and hEDS are associated with a normal life expectancy. There are, however, significant concerns with regard

Key points
⇒ Patients with hypermobility disorders (HD) present with significant gastrointestinal (GI) symptoms. Studies in this cohort of patients are retrospective, and often dysmotility has not been systematically evaluated. Thus, the true prevalence of GI dysmotility in patients with HD is currently unknown.
⇒ GI symptomatology is often due to disorders of gut–brain interaction (eg, functional dyspepsia, irritable bowel syndrome (IBS)), and in the absence of objective evidence of dysmotility or other dysfunction, a biopsychosocial model of treating symptoms is often most effective, reducing the risk of iatrogenic harm in this group of patients.
⇒ Postural tachycardia syndrome has been demonstrated in around 30% of patients with HD, with possible increased GI symptomatology if present. The potential mechanisms for this have not been fully elucidated.
⇒ There are clear guidelines for the diagnosis of mast cell activation syndrome, although at present these are frequently not followed. Biomarkers such as diamine oxidase (DAO) are not reliable enough at present to be useful, and currently there is no good quality evidence to show DAO is associated with mast cell activity or allergy.
to iatrogenic harm from invasive and non-evidence-based management strategies, often not supported by objective findings.

The association between HD and gastrointestinal (GI) symptoms was first described in 2004. Subsequently links between HD, postural tachycardia syndrome (PoTS) and GI symptoms were described, although the pathophysiology underlying this association is still unknown. It has further been postulated but unproven that mast cell activation syndrome (MCAS) is associated with HD, with again no defined pathophysiology.

Gastroenterologists are increasingly managing patients with HD and GI symptoms who additionally report multisystem symptoms, who exhibit polypharmacy for associated diagnoses such as PoTS and MCAS, and who frequently adopt dietary restrictions with the development of nutritional compromise. The investigation and management of GI symptoms for these patients is often challenging and carries the risk of causing iatrogenic harm. This article aims to review the current limited evidence base for causes of GI symptoms in HD, their association with PoTS and unclear association with MCAS. We also aim to review psychosocial comorbidities, nutritional issues and polypharmacy in this group of patients and offer a pragmatic approach to their assessment, diagnosis and management.

### GI SYMPTOMS IN PATIENTS WITH HYPERMOBILITY

There is a prevalence of between 30% and 96% for at least one GI symptom in HD, with an increased prevalence of bowel, gastroduodenal and oesophageal functional disorders when compared with age-matched controls. Table 2 overviews disorders of gut–brain interaction (DGBI) in the differential of patients presenting especially with nutritional compromise.

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### Table 1  
Hypermobility disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Joint hypermobility</td>
<td>▶ Either localised, peripheral or generalised.</td>
<td>▶ Often not pathological.</td>
</tr>
<tr>
<td></td>
<td>▶ May be symptomatic or asymptomatic.</td>
<td></td>
</tr>
<tr>
<td>Hypermobile spectrum disorder</td>
<td>▶ Generalised joint hypermobility (with allowances for age but not environmental factors).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Varied connective tissue and other symptoms (unclear evidence for true association).</td>
<td>▶ Clinical constellation of symptoms but not fulfilling diagnostic criteria for hEDS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Genetic basis unknown.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Molecular basis unknown.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Pathogenesis of associated symptoms unknown.</td>
</tr>
<tr>
<td>Hypermobile Ehlers Danlos syndrome</td>
<td>▶ Generalised joint hypermobility (with allowances for age but not environmental factors).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Clinical features suggestive of a connective tissue disorder.</td>
<td>▶ Clinical constellation of symptoms fulfilling diagnostic criteria for hEDS, some of which may suggest an acquired connective tissue disorder and some of which suggest a heritable connective tissue disorder.</td>
</tr>
<tr>
<td></td>
<td>▶ Female preponderance (unusual for a presumed autosomal dominant condition).</td>
<td>▶ Genetic basis unknown.</td>
</tr>
<tr>
<td></td>
<td>▶ Other associated symptoms (unclear evidence for true association).</td>
<td>▶ Molecular basis unknown.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Pathogenesis of associated symptoms unknown.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Ehlers Danlos syndrome types</th>
<th>Joint hypermobility, skin hyperextensibility and tissue/blood vessel fragility.</th>
<th>▶ Clinical constellation of symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>▶ Genetic basis known.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ Molecular basis known.</td>
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</tbody>
</table>

Joint hypermobility syndrome has now been incorporated into hypermobile spectrum disorder or hEDS. hEDS, hypermobile Ehlers-Danlos syndrome.
Evidence for GI dysmotility in HD is mostly from retrospective studies at tertiary neurogastroenterology centres. Abnormal gastric emptying or colonic transit is frequently described but GI motility tests were not systematically performed, and a proportion of patients remained on drugs potentially affecting gut motility during testing, especially opioids. True prevalence of GI dysmotility in HD is currently unknown.

Dysphagia is common in HD. Oesophageal physiology studies have found no increased prevalence of major oesophageal motility disorders. Functional dysphagia, not explained by structural abnormalities or major motor disorders, is frequently diagnosed.

While ineffective oesophageal motility was demonstrated in 21% of patients, this was not different to controls. Functional heartburn and oesophageal hypersensitivity are more prevalent in patients with hypermobility.

Functional dyspepsia is reported in up to 50% of patients referred to secondary care with co-existent HD, and gastroduodenal symptoms are reported in 30% of subjects in the general population fulfilling HD criteria. Accelerated and delayed gastric emptying are both reported in retrospective studies while altered accommodation was not demonstrated. Mechanisms for symptoms have not been established. Current evidence does not support an increased prevalence of gastroparesis in HD but rather increased internal sensitivity, described in patients with DGBI and HD may be contributory. Mild delayed gastric...
emptying is frequently encountered in up to a third of patients with functional dyspepsia, and the gastroparesis and functional dyspepsia overlapping constructs are not fully distinguishable by either symptoms or gastric emptying studies alone. An over-reliance on and excessive use of gastric emptying studies, particularly when performed on confounding medication such as opioids, and the resultant over labelling of gastroparesis can lead to an unnecessarily invasive and iatrogenic nutrition approach to the neglect of more comprehensive biopsychosocial management.

Case reports describe chronic intestinal dysmotility in HD but no studies have systematically investigated small bowel motility, small bowel manometry or small bowel transit in HD. A recent increase in prevalence of patients with HD on parenteral nutrition (PN) for loosely defined intestinal dysfunction has been reported.

Irritable bowel syndrome - constipation subtype (IBS-C) is common in HD. Slow colonic transit is reported in 10%–20% of patient with HD. Rectal evacuatory dysfunction (including both sensory and structural abnormalities) and descending perineum syndrome have been described.

The overall pathophysiological mechanisms for GI symptoms in HD are therefore unclear but current data suggests a high prevalence of functional GI disorders. While a hypothesis of symptoms driven by abnormal gut connective tissue is attractive, there is currently no evidence to support this, particularly as other types of Ehlers Danlos with associated hypermobility do not have a similar presentation. The role of autonomic dysfunction or mast cell activation in the pathophysiology of GI symptoms is not known despite associations with PoTS and unproven suggested association with MCAS.

### POSTURAL TACHYCARDIA SYNDROME
PoTS is a form of orthostatic intolerance which causes dizziness, palpitations, breathlessness, fatigue, syncope or presyncope on standing but also with heat, food ingestion and exertion. It is characterised by an increase in heart rate (>30 beats per minute (>40 beats per minute in teenagers) but without an associated postural drop. PoTS can be diagnosed at the bedside, although typically a tilt table test is used. Some PoTS symptoms are exacerbated by intravascular volume depletion, deconditioning and immobility. Consensus is lacking as to specific treatment recommendations. Lifestyle advice with increased salt and water intake and limiting gravitational deconditioning is first-line. Structured graduated exercise, compression stockings, withdrawing medications that might worsen PoTS and, if these measures fail, then pharmacological therapy may help. Medications typically used for PoTS are associated with GI side effects so this should be borne in mind when managing GI symptoms (table 3).

There is an association between HD and PoTS, although not exclusively. PoTS is present in up to 40% of HD and HD is present in 25% of patients with PoTS. Patients with both HD and PoTS are more likely to have more severe upper and lower GI symptoms, be symptomatic earlier, have poorer quality of life and have associated fatigue. PoTS (independent of HD) is associated with abnormal gastric emptying (rapid seen more often than delayed gastric emptying), abnormal small bowel motility and transit as well as slow colonic transit. In one tertiary centre, a retrospective observational study reported odds of having oesophageal/gastric/small/large bowel dysmotility was increased eightfold by the presence of both HD and PoTS.

<table>
<thead>
<tr>
<th>Table 3 Gastrointestinal side effects caused by medications used in patients with hypermobility</th>
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<tbody>
<tr>
<td><strong>Medication</strong></td>
</tr>
<tr>
<td>Treatment for PoTS</td>
</tr>
<tr>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>Midodrine</td>
</tr>
<tr>
<td>Iverapidine</td>
</tr>
<tr>
<td>Clonidine</td>
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<tr>
<td>Pyridostigmine</td>
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<tr>
<td>Octreotide</td>
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<tr>
<td>Common medications used for gastrointestinal symptoms</td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>Cyclizine</td>
</tr>
<tr>
<td>Ondansetron</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Treatments for MCAS</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
<tr>
<td>Sodium cromoglycate</td>
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</tbody>
</table>

GI, gastrointestinal; MCAS, mast cell activation syndrome; PoTS, postural tachycardia syndrome.
Neurogastroenterology

Nausea is a typical symptom in PoTS. If the nausea is orthostatic then treatment should be directed at PoTS itself. More commonly nausea is chronic and unrelated to posture (ie, functional nausea). This can limit the ability of patients to consume enough fluids for their PoTS, and affect eating behaviours. In one study of over 300 patients with PoTS, 10% received non-oral nutrition and hydration support, and this was more likely if they were female, underweight, on opioids and symptomatic with nausea. This highlights a subgroup of patients with PoTS with more severe symptoms, with increased risk of more invasive and iatrogenic treatment. At present, there is no evidence to support use of intravenous hydration in patients with HD and PoTS, rather, this invasive intervention may be associated with harm. Here, multidisciplinary team (MDT) management is crucial.

MAST CELL ACTIVATION SYNDROME

Mast cells (MCs) originate from myeloid precursors that migrate to all vascularised tissue, except retina and brain, to evolve into MCs. They are polymorphonuclear cells with granules made of inflammatory mediators (cytokines, histamine and proteases such as tryptase) that trigger typical clinical signs in the respiratory, cardiovascular, skin and GI systems, and could ultimately lead to anaphylaxis. They express IgE receptors that bind with parasitic antigens or allergens triggering MCs activation and release of granules. They also express many other receptors through which they receive signals from a variety of physical and chemical stimuli that could lead to activation. The term mast cell activation syndrome (MCAS) was first used in the 1990s in a hypothesis that attributed idiopathic anaphylaxis to a syndrome of MC hyperactivity. In 2007, a group of leading international experts published a consensus on classification and diagnosis of mast cell disorders. They defined MCAS as a monoclonal disease of mast cells which in some cases may progress to become systemic mastocytosis. This has evolved to include diseases in which evidence of monoclonality has not been found. Based on these guidelines, diagnosis of MCAS requires fulfilling all three criteria of: (1) spontaneous episodic presentation of signs and symptoms affecting at least two organ systems, (2) objective laboratory evidence of MC activation which requires an acute sample collected plus 20%+2 ng/mL, and (3) responsiveness to drugs targeting MCs (table 4).

These criteria provide an objective instrument to attribute pathogenicity to MCs in a given presentation. The number of patients who would fulfil these criteria is limited but over the past ten years, a large cohort with varied presentations has been labelled with MCAS without fulfilling them. Biomarkers such as diamine oxidase (DAO) have been used for diagnosis, but these markers are not recommended by expert criteria. Their measurement methods are not validated, and there is an unacceptable coefficient of variation with excessive false positives and negatives. There are no good-quality studies substantiating DAO association with MCs activity or allergy.

Such unscientific approaches hinder an understanding of true pathogenic mechanisms and development of rational management strategies. This has led to over diagnosis of MCAS in association with a great number of other conditions. In turn, this has given rise to unnecessary medicalisation, misdiagnosis and mismanagement. A common claim is an association between MCAS, HD and PoTS. In an extensive literature review, this link was ruled out. The authors concluded, ‘an evidence-based, common pathophysiological mechanism between any of the two, much less all three conditions, has yet to be described’.

PSYCHOPATHOLOGY

Prevalence studies report over 70% of patients with HD have symptoms that are psychological (anxiety, low mood) or partly psychological (fatigue, secondary deconditioning). Whether these are primary (independent of HD) or secondary (to physical symptom burden), the resultant disabilities and treatments are similar. Interventions depend on interacting symptoms and psychological interventions available locally. Clinicians should affirm the presence of psychological symptoms and persuade towards effective treatments. Reducing psychological symptoms makes patients feel better, decreases overall symptom burden, and improves engagement with gastroenterology. We would expect treated patients are less likely to request opioids and procedures that do not bring relief. Psycho-social treatments help reverse the social isolation and parallel secondary deconditioning that may compound their difficulties. It is useful on assessment to record patients’ disappointments with medical care (waiting lists, delays in investigation and diagnosis, failed

### Table 4 Criteria for diagnosis of MCAS based on a consensus report by an international mastocytosis working group and the AAAAI mast cell disorder work group report

| A | Typical signs of severe, recurrent (episodic) systemic MC (often in form of anaphylaxis or crisis) (definition of systemic: involving at least two organ systems). |
| B | Objective laboratory evidence of MC activation: preferred marker: increase in serum tryptase level (baseline to baseline plus 20%+2 ng/mL) |
| C | Response to therapy with MC-stabilising agents; drugs directed against MC mediator production or drugs blocking mediator release or effects |

All three criteria need to be fulfilled for diagnosis of MCAS. AAAAI, American Academy of Allergy, Asthma & Immunology; MC, mast cell; MCAS, mast cell activation syndrome.
treatments) and family narratives of poor medical care, including those of other family members (transgenerational experiences impact on medical interactions).

In specialist clinics, a subpopulation may include patients with disordered eating (food phobias, rarely body image preoccupations), patients with childhood trauma and/or personality difficulties, and small numbers of people seeking opioids and other drugs associated with dependency. These groups benefit from local specialised mental health services, addictions support for opioid substitution therapy, and, if available, in-house gastro psychology/psychiatry. A psychiatric assessment entails more than identifying treatable mental disorders, and should also describe the set of internal and external factors that brought the patient to this point.

A rheumatology opinion to confirm HD diagnosis and severity, informs psychosocial approaches. Psychological overlay with pain, both musculoskeletal and GI, is well described: patients may have embodiment (distress is expressed as physical sensations) and/or somatosensory amplification (lower pain thresholds, hypervigilance, visceral hypersensitivity). Identifying and addressing these psychological processes reduces morbidity and iatrogenesis: as with all functional somatic syndromes, depression is common, easily missed and treatable. Stepped psychosocial care is described for inflammatory bowel disease patients, beginning with lifestyle advice (gentle exercise, sleep hygiene, diet changes), problem solving (debt, housing, etc) then stress reduction measures (mindfulness, cognitive–behavioural therapy), through to antidepresant prescription: interventions which are also likely to benefit these patients. Evidence supports antidepressants for treating chronic primary pain, but opioids are harmful without benefit. Many psychological symptoms can be secondary to opioids including dysphoria, apathy and night time insomnia as well as the distress of constipation and anergia. A strong predictor of opioid induced constipation for non-cancer abdominal pain is up to 50%, which increases with duration of treatment. Patients with opioid induced constipation have poorer quality of life. Long-term opioid use (>3 months) in chronic, non-cancer pain does not confer benefit, with patients exposed to deleterious tolerance, addiction, premature death and narcotic bowel syndrome, adding to the burden of disease.

Tricyclic antidepressants and other gut–brain neuro-modulators (with anticholinergic properties and GI side effects) are often used for visceral pain and DGBIs in these patients. Antihistamines (some sedating and with anticholinergic properties), mast cell stabilisers (which may cause nausea), antiemetics (commonly associated with deleterious GI side effects) and treatments for PoTS and urinary symptoms (often with GI side effects) are also prescribed. Frequently, these medications are used in combination. The contribution of all these medications towards the development of GI symptoms (table 3) in these patients is likely to be significant, although there is a paucity of data in the literature. Therefore, careful consideration of potential GI effects before prescribing, and rationalisation of medication lists is paramount.

**NUTRITION MANAGEMENT IN PATIENTS WITH HD**

Dietary management is a recognised therapeutic approach for DGBIs, but an overly restrictive approach risks re-enforcing disordered eating, and should be avoided (figure 1). Eating-related symptoms leading to reduced oral intake should prompt review for specific underlying DGBIs. Medical management and nutrition support should be targeted accordingly (table 4). Nutrition support should take place within a multidisciplinary context. Oral diet and oral nutrition supplements should be optimised as the primary approach. Clinically assisted nutrition and hydration (CANH) is chiefly evidenced for objectively demonstrated malnutrition or electrolyte disturbance. CANH should not be implemented for symptom management alone, given its associated iatrogenic risks.

For malnutrition or electrolyte disturbance refractory to standard treatment, PEG feeding can be initiated by nasojejunal feeding with a view to PEG-J or direct jejunal feeding (direct PEJ, direct balloon jejunostomy or surgical jejunostomy).
Neurogastroenterology

in the longer-term if tolerated. A note of caution is that enteral tube feeding might impair both nutritional rehabilitation and psychological recovery if there is a component of an avoidant restrictive food intake disorder. In addition to the morbidity and mortality risks of insertion of percutaneous feeding tubes, these are also associated with skin healing, infection and over granulation complications to which this patient group might be more susceptible.

Failure to tolerate small intestinal enteral feeding is frequently due to pain or discomfort, rather than due to failure of small intestinal muscle or absorptive function. There is no current evidence for the presence of malabsorption specifically in HD. There is a significant overlap of hypermobility with fibromyalgia, and for the latter, there is growing evidence for peripheral and central sensitisation underlying pain sensitivity. In a chronically sensitised state, there is a likelihood of developing fear avoidance to food provoked symptoms. There may be a poor symptom association probability between rate and volume of enteral feed and pain provoked symptoms. Chronic pain management with a focus on neuropathic pain agents, and chronic pain psychology with a rehabilitative focus, are therefore important components of multidisciplinary care. Rehabilitation services are largely configured around the outpatient setting once nutritional stability has been achieved, however, in-patient pain and liaison psychiatry/psychology input should also be solicited during the nutrition stabilisation period.

Compared with the rest of Europe, there is a significantly escalating rate of referral of patients with HD to Intestinal Failure Units for consideration of PN in the UK. This is concerning since PN is typically detrimental to quality of life and can have life-threatening complications. There is evidence that patients with a functional diagnosis who are on opioids and cyclizine are at higher risk of iatrogenic harm. PN may become a pragmatic necessity when otherwise faced with severe life-limiting malnutrition and intolerance of enteral feeding. This should be implemented together with appropriate psychological support working in close collaboration with the clinical team.

Figure 1 Potential contributors to developing and maintaining disturbed eating behaviours and significant weight loss seen in HD, adapted from Bulbena et al.41
Once CANH has been implemented, the development of any iatrogenic complications should prompt re-evaluation of the risk/benefit balance of the intervention. Moreover, once nutrition has stabilised, re-exploring optimised oral approaches and less invasive forms of CANH should be considered, with a view to weaning to the least invasive approaches possible in the longer term. 

CONCLUSIONS

GI symptoms, associated physical and psychological comorbidities and nutritional challenges all have a significant effect on morbidity and quality of life in HD. The pathophysiology of GI symptoms appears to be mediated via the gut–brain axis. This, in combination with increased rates of other functional disorders, suggests a multidisciplinary, biopsychosocial model of care is required in this group of patients.

PoTS and MCAS are often claimed to be associated with HD, but the mechanism of this association is not currently evident, especially for MCAS. Thus, in addition to the medication burden prescribed for HD, GI symptoms and psychopathology, adding medication to treat PoTS and MCAS increases the risk of further iatrogenic harm from polypharmacy. Cardiology and immunology should lead on confirming and managing these associated diagnoses, in addition to rheumatology for HD itself, emphasising the value of a rehabilitative approach.

Nutritional issues require an MDT strategy, aiming to stabilise and then safely manage nutrition via the least invasive approach, minimising risks of CANH-related iatrogenic harm.

Fragmentation of care occurs readily in these patients, especially if care is divided between several centres, and between the public and private sector. This also inevitably increases the risk of iatrogenic harm. Management of GI symptoms, psychopathology, PoTS, MCAS and nutritional issues optimally requires an integrated strategy between primary care and multiple specialties including gastroenterologists, psychiatrists, psychologists, rheumatologists, cardiologists, immunologists, urologists, orthopaedics, dietitians, pharmacists and physiotherapists.

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REFERENCES

11 Abdul-Razaq HB, Sveis M, Siirim R. No increase in oesophageal dysmotility or hiatus hernias in patients with hypermobility spectrum disorders and dysphagia compared to non-hypermobility controls: a two-centre case-control study. Neurogastroenterol Motil 2021;33:49.


75
Neurogastroenterology


