



# Nutritional Implications of Patients with Dysautonomia and Hypermobility Syndromes

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## Abstract

**Purpose of Review** Dysautonomia and hypermobility syndrome are two distinct but often overlapping clinical conditions that are recognized for their complex multiorgan system afflictions. The purpose of this review is to investigate dietary strategies to reduce symptoms and augment quality of life in this growing patient population.

**Recent Findings** There is increasing evidence supporting dietary modifications to include food rich in probiotics and prebiotics, along with fiber supplements to reduce gastrointestinal symptoms. Adequate salt and fluid intake may reduce orthostatic hypotension symptoms. Dietary supplements may help with osteoarticular, musculoskeletal, and fatigue symptoms.

**Summary** Individualized diet strategies and supplements can reduce the multiorgan system symptoms observed in dysautonomia and hypermobility syndrome.

**Keywords** Dysautonomia · Hypermobility Syndrome · Nutrition · Orthostatic · POTS · Ehlers-Danlos

## Introduction

Hypermobility syndromes are connective tissues disorders that often present with autonomic dysfunction [1–3]. Autonomic dysfunction, also called dysautonomia, is any change

in the autonomic nervous system (ANS) that adversely affects health [4, 5]. Autonomic dysfunction can impact major organ systems including nervous, circulatory, respiratory, endocrine, and digestive and excretory systems [6–8]. This patient population is increasingly recognized for their complex gastrointestinal symptoms. Further understanding of the nutritional implications in this subgroup of patients will be integral in providing optimal multidisciplinary care and improving quality of life, while reducing morbidity and healthcare utilization.

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## Classification of Dysautonomia and Hypermobility Syndromes

Dysautonomia is associated with several diseases that can be categorized into primary versus secondary. Primary conditions of dysautonomia include neurogenic syncope, postural orthostatic tachycardia syndrome (POTS), familial dysautonomia (FD), and multiple system atrophy. Of the four major conditions of primary dysautonomia, postural orthostatic tachycardia syndrome (POTS) appears to have the most impact on the gastrointestinal system and nutritional status [9]. Several diseases are associated with secondary dysautonomia including gastrointestinal conditions

such as inflammatory bowel disease, celiac, and eosinophilic esophagitis; neurological and autoimmune conditions such as Parkinson's, muscular sclerosis, and lupus; and infections such as HIV, Lyme disease, and COVID-19 [2, 5, 10–16]. Further studies are required to elucidate the pathophysiology and clinical impact of dysautonomia in these conditions.

Hypermobility syndromes are a complex and multisystemic spectrum of conditions. Hypermobility can be asymptomatic or can present with joint manifestations (arthritis, arthralgia) and soft tissue injuries. When associated with clinical symptoms, the condition is termed joint hypermobility syndrome (JHS) [17]. The symptoms of JHS are considered benign and distinguished from other potentially life-threatening connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome (EDS) [18]. EDS is a group of heritable disorders, characterized by non-inflammatory conditions of connective tissue that present with musculoskeletal symptoms, hyperflexible joints, and hyperelastic skin [19]. Recent literature suggests that clinically, JHS is similar to a subgroup called Ehlers-Danlos syndrome hypermobility type (EDS-HT) [2]. Extra-articular manifestations of JHS include skin laxity and fragility, ocular ptosis, varicose veins, Raynaud's phenomenon, developmental motor delay, fibromyalgia, and low bone density [20, 21].

## Epidemiology and Demographics

Postural orthostatic tachycardia syndrome (POTS), recognized in 1993 by Ron Schndorf and Phillip Low, is among the most common causes of chronic orthostatic intolerance [9, 22]. POTS is diagnosed when positional change from supine to upright posture results in a sustained heart rate increase of  $>30$  beats per minute (or  $>40$  in patients  $<19$  years of age) with symptoms of orthostatic intolerance (dizziness, lightheadedness, blurry vision, tremulousness, weakness) [23–25]. The symptoms need to be chronic ( $>3$  months) and the observed tachycardia should be in the *absence* of orthostatic hypotension ( $>20/10$  mm Hg). POTS afflicts approximately 500,000 Americans, most of whom are of white race (93%) and female sex of child bearing age (94%) [26, 27]. The condition can result in significant financial cost to the individual. In a study of 4468 individuals ( $>18$  years old) diagnosed with POTS, about 75% reported inability to work for at least a week and 67% had to modify their employment responsibilities due to symptoms [28].

The prevalence of joint hypermobility syndrome (JHS) varies in literature due to differing diagnostic criteria. It is generally recognized that the condition is more prevalent in those of Asian or African descent, children and adolescents, and in females [29–31]. A study of 655 subjects (482 females) US college students estimated that 12.5% have generalized joint hypermobility [32]. Although the prevalence of JHS differs

across races and age, this condition is likely underdiagnosed, and the number of individuals impacted by this condition is expected to be higher. Similar to JHS, Ehlers-Danlos syndrome is considered an underdiagnosed condition. It is estimated that 1 in 5000 individuals have Ehlers-Danlos syndrome (all types) [33].

## Overlap of Dysautonomia and Hypermobility Syndromes

The association between hypermobility conditions and dysautonomia is increasingly demonstrated in literature and recognized clinically. Possible mechanisms to explain dysautonomia in EDS include adreno-receptor hyperresponsiveness, peripheral neuropathy, and molecular defect in blood vessel connective tissues [2, 18, 34]. A study of 48 subjects with JHS (1998 Brighton criteria) demonstrated 78% (21/27) experienced orthostatic intolerance compared with 10% (2/21) of controls [2]. Subjects with JHS also reported greater increase in systolic blood pressure after cold pressor test ( $10 \pm 10$  mm Hg vs  $11 \pm 13$  mm Hg) with evidence of  $\beta$ -adrenergic and  $\alpha$ -adrenergic hyperresponsiveness compared to controls. Celletti et al. demonstrated in 25 individuals diagnosed with JHS or Ehlers-Danlos syndrome hypermobility type (EDS-HT), 48.6% subjects showed postural orthostatic tachycardia on head-up tilt table test and 31.4% had symptoms of orthostatic intolerance [35]. At resting state, these JHS/EDS-HT subjects also showed significantly higher baroreflex sensitivity compared to controls. A study of 84 subjects with EDS-HT showed these subjects had lower total peripheral resistance and higher heart rate at head-up tilt (70 degree) tests [36].

There is increasing literature reporting the concurrent diagnoses and overlapping symptoms of POTS and EDS-HT. Wallman et. al. reviewed 109 medical records and demonstrated that in subjects with POTS, about 18% also had EDS compared to 0.02% in the general population [37]. The odds ratio of EDS in POTS versus non-POTS patients is 4.9. Individuals with POTS and JHS present with symptoms at an earlier age (23 years old  $\pm 13$  versus 41 years old  $\pm 12$ ) compared to individuals with POTS without JHS [38]. Beyond dysautonomia, individuals with JHS/EDS-HT have a range of symptoms that overlap with other conditions such as chronic pain syndromes, chronic fatigue syndrome, anxiety disorder, pelvic floor dysfunction, and exocrine gland dysfunction [39].

## Gastrointestinal Symptoms in Dysautonomia and Hypermobility Syndromes

Gastrointestinal (GI) symptoms are highly prevalent in individuals with JHS/EDS-HT and contribute to significant functional debility and adverse nutritional consequences. In

a pilot study in 2010, Castori et al. found 18/21 (86%) subjects with JHS/EDS-HT reported GI symptoms that included constipation/diarrhea (33.3%), abdominal pain/discomfort (61.9%), gastroesophageal reflux (57.1%), and dyspepsia (66.7%) [40]. The same year, Zarate et al. reported frequent GI symptoms in 21 subjects with JHS/EDS-HT, including dysphasia (14.3%), gastroesophageal reflux (52.4%), bloating (57.1%), vomiting (57.1%), recurrent abdominal pain 85.7%, and constipation/diarrhea (76.2%) [41]. Zarate et al. also found abnormal esophageal manometry (33.3%), abnormal 24-h pH-ambulatory monitoring (33.3%), delayed gastric emptying (80%), abnormal small bowel manometry (44.4%), and abnormal colorectal transit (100%). Fikree and colleagues reported that subjects with JHS were found to have an odds ratio (OR) 1.66 for heartburn, OR 2.02 for water brush, and OR 1.74 for postprandial fullness compared to non-JHS controls [42]. A positive, linear correlation between the severity of JHS and GI symptoms were observed in this population. In a recent retrospective review, Zhou et al. found that 35% of EDS-HT patients who underwent breath testing had small intestinal bacterial overgrowth (SIBO), of which 92% were methane positive, while only 35% were hydrogen positive. Unlike SIBO in the general population, EDS-HT patients with SIBO were more likely to be constipated compared to EDS patients without SIBO (50.00 vs. 26.53%,  $p=0.042$ ) [43].

Dysautonomia further exacerbates GI complications in EDS-HT individuals. The autonomic nervous system controls the “fight or flight” versus “rest and digest” response [44]. An imbalance of this binary state causes individuals with EDS-HT an inability to be in the “rest and digest” state when appropriate. There is increasing literature demonstrating that dysautonomia is a major factor to a spectrum of GI complaints [41–45]. Dysbiosis and dysregulation of gut-related immune function may be linked to a higher prevalence of food allergies and inflammatory or autoimmune disorders observed in EDS-HT individuals [46, 47].

## Nutritional Management

Identifying and correcting nutritional deficiencies is the cornerstone of nutritional management for patients with dysautonomia and/or JHS/EDS-HT. Although literature on nutritional management of this population is limited, the spectrum of symptoms observed in this population have been demonstrated to be significantly influenced by nutritional status and dietary intake. Primary nutrition recommendations most often include diet modification, nutrition support therapies, and micronutrient supplementation to improve or maintain nutrition status when symptoms have resulted in suboptimal oral intake, altered utilization of nutrients, and significant weight loss [48••]. As with any chronic disorder,

a thorough nutrition assessment that includes dietary history, weight history, past medical and surgical history, medication/supplement review, GI function, and a comprehensive nutrition focused physical exam is necessary to determine appropriate nutrition therapies.

There is theorizing in the literature that alternative therapies including modified diets and nutritional supplements may improve symptoms related to dysautonomia and JHS/EDS-HT; however, given the extrapolative nature and lack of empirical investigation, these nutritional suggestions should be considered low-level recommendations [39]. An individualized plan of nutritional management that includes careful monitoring of symptoms with a multidisciplinary approach that includes gastroenterology, nutrition, psychiatry, and pain management, and neurology is likely to yield the best results [49••].

## Diet Modifications

The spectrum of gastrointestinal symptoms experienced by individuals with dysautonomia and JHS/EDS-HT can be ameliorated through various nutritional supplements and avoidance of specific foods (Table 1). These recommended modifications may not have been studied in patients with dysautonomia but are extrapolated from studies in subjects with conditions that have similar symptoms as those with dysautonomia and JHS/EDS-HT.

Diarrhea and constipation are two common GI symptoms of individuals with dysautonomia and HMS/EDS-HT. Soluble fiber supplements not only reduce diarrhea but have also demonstrated long-term protective effects against metabolic disorders, cardiovascular disease, and colon cancer along with promoting bowel regularity [11, 50]. A low FODMAP (fermentable oligo, di, mono-saccharides, and polyol) diet has been shown to reduce symptoms of diarrhea, bloating, and flatulence in individuals with irritable bowel syndrome (IBS) by 50–80% [51]. Similarly, a gluten-free diet has been demonstrated to reduce diarrhea and abdominal discomfort in some individuals with IBS [52]. Probiotics such as *Lactobacillus* GG and *Bifidobacterium lactis* can also reduce frequency of diarrhea [53]. For individuals who experience constipation, fiber supplementation has been demonstrated to increase stool frequency [54]. It should be noted that the impact of fiber on stool consistency and pain with defecation is marginal.

Optimization of the gut microbiome may promote digestion and reduce GI symptoms in this population. The gut microbiome plays an increasingly recognized role in digestion, gut inflammation, and absorption of nutrients [55, 56]. These beneficial bacteria in the gut assist in the digestion of resistant starches and lipids, synthesis short-chain fatty acid, and absorption of essential fat soluble vitamins (A,

**Table 1** Dietary recommendations for gastrointestinal, orthostatic hypotension, osteoarticular, musculoskeletal pain, and fatigue in individuals with dysautonomia and hypermobility syndrome

Symptoms	Recommendations
Gastrointestinal	Diarrhea/flatulence/bloating <ul style="list-style-type: none"> <li>● FODMAP diet [51]</li> <li>● Gluten-free diet [52]</li> <li>● Soluble fiber [11, 50]</li> <li>● Probiotic [53, 60]</li> <li>○ <i>Lactobacillus GG</i></li> <li>○ <i>Bifidobacterium lactis</i></li> <li>● SIBO treatment (i.e., rifaximin) [43]</li> </ul> Constipation <ul style="list-style-type: none"> <li>● Fiber supplement [54]</li> <li>● SIBO treatment, including methane positive [43]</li> </ul> Normobiosis <ul style="list-style-type: none"> <li>● Probiotic-rich foods [59••]</li> <li>○ Yogurt, miso, kimchi</li> <li>■ <i>Lactobacillus</i></li> <li>■ <i>Clostridium</i></li> <li>■ <i>Bifidobacterium</i></li> <li>■ <i>Streptococcus</i></li> <li>● Prebiotics [63–64, 99]</li> <li>○ Inulin</li> <li>○ Fructooligosaccharide (FOS)</li> <li>○ Lactulose</li> <li>○ Milk oligosaccharide</li> <li>○ Beans, garlic, unripe bananas</li> <li>● Supplements</li> <li>○ 5000U vitamin D3 [82]</li> <li>○ 750–1000 mg/day vitamin C (EDS-HT) [83]</li> <li>○ 1500 mg/day methylsulfonylmethane [82]</li> <li>○ 3 mg/day silica [82]</li> <li>○ Vitamin B12 [84]</li> <li>○ Vitamin B1 (thiamine) [10]</li> <li>○ Antioxidants [63]</li> <li>○ Fiber</li> </ul> Avoid <ul style="list-style-type: none"> <li>● Artificial sweeteners</li> <li>● High fructose</li> <li>● Alcohol</li> </ul>
Orthostatic hypotension	Salt [75••, 76, 77] <ul style="list-style-type: none"> <li>● American Journal of Cardiology (2017)</li> <li>○ 6–9 g (100–150 mmol) per day</li> <li>● American Society of Hypertension (2013)</li> <li>○ 6–10 g NaCl</li> <li>● American Family Physician (2011)</li> <li>○ Salty food and 0.5–1 g tablets</li> </ul> Fluid [75••, 76, 77] <ul style="list-style-type: none"> <li>● American Society of Hypertension (2013)</li> <li>○ 1.5–2L</li> <li>● European Society of Cardiology (2018)</li> <li>○ 2–3L fluids</li> </ul> Size & Temperature [74] <ul style="list-style-type: none"> <li>● Small, frequent meals</li> <li>○ 6 smaller meals &gt; 3 large</li> <li>● Room temperature</li> </ul>
Osteoarticular	Joint [89–91] <ul style="list-style-type: none"> <li>● 1500 mg/day glucosamine</li> <li>● 1200 mg/day chondroitin sulfate</li> <li>● 228 mg/day manganese ascorbate</li> </ul>
Musculoskeletal pain	MSK [92, 93] <ul style="list-style-type: none"> <li>● 250 mg /day carnitine</li> <li>● 100 mg/day coenzyme Q10</li> </ul> Reducing Inflammation [88] <ul style="list-style-type: none"> <li>● 240 mg/day <math>\gamma</math>-linolenic acid</li> </ul>

**Table 1** (continued)

Symptoms	Recommendations
Fatigue	Supplements [92, 96, 98] ● Coenzyme Q10 ● Magnesium ● Nicotinamide adenine dinucleotide (NADH) ● Alpha-lipoic acid

D, E, and K) and minerals (Ca, Mg, and Fe) [54, 57, 58]. To reestablish normobiosis, patients should eat foods high in probiotics (yogurt, miso, kimchi) that contain organisms such as *lactobacillus*, *clostridium*, *bifidobacterium*, and *streptococcus* [59••, 60, 61]. These organisms have been shown to promote digestion and reduce gut inflammation in conditions such as IBD and celiac disease. Prebiotics, defined as compounds that are metabolized by beneficial gut bacteria, are another source to promote gut health [59••, 62]. Food rich in prebiotics include inulin, fructooligosaccharide (FOS), lactulose, milk oligosaccharide, beans, garlic, and unripe bananas. Supplements of antioxidants and fiber can further support growth of beneficial gut bacteria [63, 64].

Avoidance of certain foods may prevent dysbiosis. Processed foods, including refined carbohydrates, and those high in salt such as cured meats, contribute to dysbiosis [65]. Artificial sweeteners may promote harmful gut organisms like *Proteobacteria*, and contribute to gut inflammation, glucose intolerance, and breakdown of the GI intestinal barrier that result in a “leaky gut” [66–68]. A dysfunctional GI intestinal barrier that allows “leakage” of material in and out of the body has been linked to several GI symptoms including bloating, cramps, food allergies, gas, and headaches [69••]. A “leaky gut” may be associated with multiple sclerosis, inflammatory bowel disease, depression and other mood disorders, and autoimmune conditions. Similarly, a diet high in fructose and alcohol consumption has been linked to dysbiosis and increased gut permeability [70, 71].

### Salt and Fluid Intake

Various nutritional strategies can be applied to reduce orthostatic symptoms experienced by individuals with primary dysautonomia or JHS/EDS-HT. Mathias et al. demonstrated that water intake of 2–2.5L/day and salt ingestion >8g (150 mmol/day) can improve orthostatic hypotension [72]. Adequate water intake can reduce changes in blood pressure and heart rate in subjects with severe orthostatic hypotension [73]. Subjects who drank 480 mL of tap water at room temperature within 5 min demonstrated less blood pressure decrease ( $22 \pm 10/12 \pm 5$  mm Hg) compared to those without drinking water ( $43 \pm 36/20 \pm 13$  mm Hg) with position change. This is believed to be secondary to a rapid pressor response in individuals with autonomic failure.

Puvi-Rajasingham et al. demonstrated that in subjects with primary chronic autonomic failure, having 6 smaller meals instead of three larger meals resulted in fewer symptoms of dizziness and lightheadedness with positional changes [74].

Increasing salt intake in individuals with orthostatic hypotension has been recommended by the 2017 ACC/AHA/HRS guideline and the American Family Physician, although with varying amounts [75••, 76–77]. Low (2008) and colleagues studied subjects with neurogenic orthostatic hypotension and reported that salt supplementation is essential [78]. After checking 24-h urinary sodium, individuals with value <170 mmol can be supplemented with 1–2g of sodium tablets three times a day. Figueroa et al. proposed salty soup and approximately 8 oz. serving of fluid over half a day or 2 g salt tablets three times a day with a minimum of eight 8-oz serving of fluid over a day to reduce orthostatic decompensation [79]. It should be recognized that there is low-quality evidence that increased salt intake reduces orthostatic intolerance [77]. A meta-analysis of 14 studies with 391 subjects demonstrated that increase salt intake resulted in higher systolic blood pressure by 12 mmHg and fewer reported symptoms of orthostatic intolerance. Although long-term empirical investigation is needed in subjects with dysautonomia to assess the full impact of dietary salt on symptoms, increasing the quantity of salt in diet may reduce the frequency and severity of orthostatic hypotension in this population.

### Micronutrients

Individuals with EDS-HT and dysautonomia are at risk for micronutrient deficiencies, due to limitations in dietary intake and bacterial overgrowth and may require either oral or parenteral supplementation. EDS-HT patients are known to have low vitamin D serum levels [80, 81]. It is recommended that EDS-HT individuals take 5000U daily of vitamin D3 (cholecalciferol) year-round or at a minimum during non-summer months. To reduce complications of skin fragility and promote wound healing, individuals with EDS-HT should take 750–1000 mg/day vitamin C and 1500 mg/day of methylsulfonylmethane (MSM) plus silica 3 mg/day [82]. Vitamin C, also called ascorbic acid, is a cofactor in collagen synthesis and is rapidly consumed in the wound healing process [83]. It is also an antioxidant and suppressor of pro-inflammatory processes. Individuals with POTS have been



shown to be deficient in B12 and B1. B12 deficiency was proven to be significantly lower in children with POTS and B12 supplements may reduce orthostatic symptoms in this population [84]. Vitamin B1 (thiamine), is a water-soluble vitamin that is integral to energy metabolism. Thiamine supplement in individuals with experiencing dysautonomia can help promote cell growth, function, and development [10].

## Non-oral Nutrition and Hydration Support

In some instances, despite optimized medical therapy, patients with primary dysautonomia or JHS/EDS-HT are unable to meet their nutrition and hydration needs orally. Individuals with poor nutrition status may require intravenous hydration, enteral nutrition or even parenteral nutrition support. In a retrospective cohort study of 332 subjects at a tertiary care hospital, patients with POTS were followed for 7 years [49••]. In the cohort, a subset of 32 patients required nutrition support, of which 66% required intravenous fluids, 59% required enteral nutrition, and 28% required parenteral nutrition. Six of the 32 patients required all three forms of nutrition support throughout the study period. Severe GI symptoms, such as nausea and vomiting, diarrhea, constipation and abdominal pain, were more prevalent in patients receiving nutrition support and GI transit studies were more likely to indicate delayed gastric emptying, indicating that GI dysmotility is a significant factor in need for nutrition support.

## Dietary/Nutritional Supplements

### Osteoarticular Joint Pain

Individuals with JHS/EDS-HT commonly experience joint symptoms that result in functional impairment, often requiring analgesic use and corrective surgery [85]. Musculoskeletal pain is derived from acute, recurrent, or chronic inflammation of soft tissues leading to bursitis, synovitis, fasciitis, or tendinitis [42, 86]. Castori et al. demonstrated that the prevalence of arthralgias and back pain in EDS individuals increased from approximately 30% in children to >80% in adults over 40 years old [87]. The frequency and severity of MSK pain is dependent on general lifestyle, physical activity, trauma/surgery, and co-morbidities [88]. The natural history of JHS/EDS begins with sprains, dislocations, growing pain which progresses to recurrent arthralgias, back pain, radiographic osteoarthritis, and spondylosis. In the third to fourth decade of life, chronic arthralgias, back pain, tendon/ligament degenerations, and widespread rigidity is common. In early stage, pain is commonly localized at small to large joints and is sensed by nociceptors. With recurrent and progressive injury, individuals with JHS become unable

to localize their pain. In advanced forms of JHS/EDS-HT, analgesic medication alone is insufficient to manage pain.

Nutritional therapies for osteoarticular joint pain in individuals with JHS/EDS-HT are wide ranging. For joint injury and arthritis, 1500 mg/day of glucosamine is recommended [89, 90]. Glucosamine is a sugar-related nutrient used by the body to synthesize complex molecules, which are necessary to maintain, support, and repair connective tissue and joints. Glucosamine or chondroitin have demonstrated reduction in joint space narrowing [89–91]. Although not yet studied in JHS/EDS-HT individuals, chondroitin sulfate (1200 mg/day) and manganese ascorbate (228 mg/day) may reduce degenerative joint disease of knee or low back.

### Musculoskeletal and Neuropathic Pain

Musculoskeletal pain is common and present within the first decade with exertional or post-exertional myalgia/cramps and mild hypotonia in JHS/EDS-HT. In the second to third decade of life, recurrent myalgias and focal muscle hyperalgesia may progress to chronic myalgias, fibromyalgia, and muscle weakness [88]. Neuropathic pain can present as peripheral paresthesia, allodynia, generalized muscle hyperalgesia (including fibromyalgia), and dysesthesias.

For general muscle weakness and fibromyalgia, a supplement of 250 mg/day of carnitine and 100 mg/day coenzyme Q10 (CoQ10) can improve symptoms [92, 93]. Carnitine is a natural compound that is an essential cofactor in fatty acid metabolism. CoQ10 is a cofactor for production of adenosine triphosphate (ATP), an integral compound providing energy to cells such as muscles. In a meta-analysis of 12 studies with 75 subjects, CoQ10 supplement significantly reduced statin-associated muscle weakness, cramp, fatigue, and pain [94]. For general inflammation,  $\gamma$ -linolenic acid at 240 mg/day is recommended [88].  $\gamma$ -linolenic acid is an essential fatty in cell membranes and a precursor to eicosanoids [95]. Eicosanoids are compounds integral to the development and maturation of the immune system and inflammatory response. Supplement of  $\gamma$ -linolenic acid may provide the necessary precursors to repair the inflammatory and gut microbiome dysfunction.

### Fatigue

Fatigue is common in patients with JHS/EDS-HT. It may present in the first decade of life and progress to poor sleep and post-exertional dyspnea [88]. Fatigue can progress to severe post-exertional malaise and disabling morning fatigue. Supplements such as CoQ10, magnesium, nicotinamide adenine dinucleotide (NADH), and alpha-lipoic acid may ameliorate fatigue [96]. A meta-analysis demonstrated improvement in fatigue with CoQ10 supplementation among heart failure, multiple sclerosis, fibromyalgia, and healthy

individuals [97]. In subjects with chronic fatigue syndrome, NADH taken in combination with CoQ10 has also been proven to improve fatigue [92]. Magnesium levels have been shown to be lower in individuals with chronic fatigue syndrome compared to controls [98]. Furthermore, Cox et al. demonstrated in a randomized, double-blind study that intramuscular magnesium sulphate weekly for 6 weeks resulted in less pain, improved emotional state, and overall higher energy levels compared to placebo.

## Conclusion

Dysautonomia and JHS/EDS-HT are independent but often overlapping conditions that are increasingly recognized clinically for the multisystem complexity in their presentation and symptoms. Among the range of ailments, gastrointestinal, orthostatic, osteoarticular, musculoskeletal pain, and fatigue are the most prevalent and debilitating. While there are pharmacologic therapies to address specific symptoms, nutritional management remains a cornerstone of optimizing this patient population's overall nutritional status and quality of life (Table 1). GI symptoms such as diarrhea and constipation can be reduced with increasing soluble fiber, food rich in pre and probiotics, FODMAP, or gluten-free diet. Furthermore, these modifications will promote normobiosis of the gut resulting in improved absorption and reducing leaky intestinal barrier. Orthostatic hypotension can be ameliorated with salt (6–10 g per day) and drinking (1.5–3L) fluids per day. Supplements such as glucosamine, carnitine, CoQ10 can reduce systemic symptoms of osteoarticular inflammation, musculoskeletal pain, and severe fatigue, respectively. These recommendations may be extrapolated from studies in populations afflicted by similar symptoms as those with dysautonomia, and further investigations are required to elucidate the pathophysiology of symptoms and specific benefits of nutritional support in individuals with dysautonomia and hypermobility syndrome.

**Data Availability** Data derived from public domain resources.

## Compliance with Ethical Standards

**Conflict of Interest** None.

**Human and Animal Rights and Informed Consent.** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Ethics approval** This literature review has not been submitted to more than one journal for consideration. To the best of authors' knowledge, all data have been cited by the original publisher to maintain integrity of scientific discovery. We will correct any fundamental errors identified in this article.

**Consent to participate.** All authors whose names appear on the submission made substantial contributions to the submitted manuscript.

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Papers of particular interest, published recently, have been highlighted as:

### ●● Of major importance

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