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Review Article

Gastrointestinal Manifestations of Hypermobile Ehlers-Danlos Syndrome and Dietary Approaches Related to Their Management

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Abstract

Although hypermobile Ehlers-Danlos Syndrome and hypermobility spectrum disorders are best known for musculoskeletal manifestations such as tendon ruptures, tendonitis, osteoarthritis, and chronic joint pain, other comorbidities are common in these conditions, including gastrointestinal dysfunction. Gastrointestinal symptoms experienced by those with hypermobile Ehlers-Danlos Syndrome and hypermobility spectrum disorders are primarily functional and nonlife threatening, but negatively impact quality of life. Some symptoms associated with these conditions include bloating, reflux, and abdominal discomfort which can potentially be managed using dietary approaches. Limited evidence suggests that protein and vitamin D intakes are lower in those with hypermobile Ehlers-Danlos Syndrome and hypermobility spectrum disorders, and these nutrients are well known for playing critical roles in musculoskeletal system making them points of emphasis for researchers and clinicians involved with hypermobile Ehlers-Danlos Syndrome and hypermobility spectrum disorders. More research is needed to establish the best dietary approaches to manage the gastrointestinal symptoms related to these conditions and to determine if there are other shortfall nutrients.

Keywords: Ehlers-Danlos Syndrome; Hypermobility; Hypermobility Spectrum Disorder; Nutrition; Quality of Life

Introduction

The Ehlers-Danlos Syndromes (EDS) are a group of 13 heritable connective tissue disorders that affect the skin, bones, blood vessels, and gastrointestinal tract among other organs and tissues. The effects of EDS can range from mildly loose joints to life-threatening complications. Joint hypermobility is a common symptom of EDS but is especially prominent in hypermobile Ehlers-Danlos Syndrome (hEDS) where it can lead to generalized joint hypermobility, musculoskeletal manifestations, and mild skin involvement, along with the possible presence of several comorbid conditions [1]. In addition, it must be noted that there are acquired forms of hypermobility that may be present in gymnasts, ballet dancers, cheerleaders, wrestlers, and other athletes or performers, where hypermobility is trained, and this is not suggestive of a connective tissue disorder such as EDS [2]. In fact, genes have been identified for 12 types of EDS, all but hEDS [3].

Due to overlap in phenotype, particularly joint hypermobility, among EDS subtypes, a genetic diagnosis is preferred for diagnosing all subtypes, except for hEDS which as noted does not yet have identifiable genetic markers. Nonetheless, patients with suspected hEDS should undergo genetic testing to rule out other subtypes of EDS [4]. Diagnosis of hEDS is largely based on the Beighton Score, a test for generalized joint hypermobility, but includes two other criteria that must be met. The diagnostic guidelines for hEDS were edited in 2017 and include the Beighton Score, but also major

and minor criteria that must be met for diagnosis [3]. These criteria are described in more detail by Malfait and colleagues (2017) [3].

Similar to hEDS, Hypermobility Spectrum Disorders (HSD) are poorly understood connective tissue disorders. HSD includes a complete spectrum ranging from asymptomatic hypermobility to hypermobility affecting only one joint, to generalized joint hypermobility, subluxations, and dislocations. It is common for patients with symptomatic joint hypermobility, but do not meet hEDS diagnostic criteria to be diagnosed with HSD. Due to the lack of a genetic marker at this time for hEDS or HSD, these diagnostic groups are often grouped together [5]. Also as the result of the lack of a clear diagnostic test for hEDS and HSD, the exact prevalence of hEDS and HSD is unknown. EDS has been estimated to impact 1 in 5,000 people worldwide, but evidence to support this statistic is limited [6]. Researchers estimate that hEDS and HSD affect 10 times as many people, impacting as many as 1 in 500 people; this is based on an epidemiological study out of Wales which found a combined diagnosed prevalence of hEDS and HSD of 194.2 per 100,000 or 1 in 500 people [7]. Females are predominantly affected by hEDS. This disparity may be due to females being diagnosed due to a higher severity of symptoms than men as the result of greater joint stability in men due to muscle mass and ligament stiffness, and females being more likely to engage in the medical system earlier than men [8]. Without a definitive diagnostic test, it is common for patients to go undiagnosed until they suffer from noticeable symptoms, and thus it can be assumed that the actual prevalence of hEDS and HSD are much higher than what is reported for the other 12 EDS subtypes.

Although best known for musculoskeletal manifestations such as tendon ruptures, tendonitis, muscle and ligament tears, muscle tension and spasms, osteoarthritis, and chronic joint pain in both children and adults, other comorbidities are common in those with hEDS, including widespread chronic pain, autonomic dysfunction, psychological disorders, mast cell activation syndrome, and gastrointestinal dysfunction [5]. Gastrointestinal (GI) symptoms experienced by affected patients are primarily functional and nonlife threatening, but impact quality of life. The frequency of GI symptoms in people with hEDS and HSD is high and includes abdominal pain, bloating, nausea, chronic gastritis, reflux symptoms, vomiting, constipation, and diarrhea. Gastroesophageal Disease (GERD), Irritable Bowel Syndrome (IBS), functional constipation, gastroparesis, and dysmotility have also been reported by patients [9]. Anatomical abnormalities attributed to structural changes in collagen located in the smooth muscle of the GI tract may also present as diverticulosis, prolapse, and rectoceles. Celiac disease is also reported to be more prevalent within the hEDS patient population [10]. Changes to dietary intake offer a way to manage the symptoms of hEDS and HDS, in particular its GI manifestations. In this work, we detail the GI manifestations of hEDS, as well as the current literature on dietary and supplement interventions to treat hEDS and HSD GI symptoms.

Methods

This narrative review utilized the PubMed database and the following MeSH terms: “Ehlers-Danlos AND nutrition”, “Ehlers-Danlos AND vitamin D”, “hypermobility AND nutrition”, and “Ehlers-Danlos Syndrome AND nutrition.”

Gastrointestinal Symptoms and Conditions

The cause of GI symptoms in hEDS patients is not fully understood. There are multiple hypotheses about GI disorders in this patient population which include connective tissue laxity in the GI tract, functional consequences of connective tissue laxity, and/or the involvement of the nervous system, since dysautonomia is common in this patient population and further exacerbates GI complications in hEDS and HSD [11-13]. We are not aware of any studies directly examining the roles of collagen and the nervous system in the GI manifestations of hEDS and HDS. Thus, the exact etiology is unknown, and the proposed hypotheses remain limited. Although the causes of the GI symptoms of hEDS and HSD are opaque, it is clear that people with hEDS or HDS are more likely to report GI symptoms and/or have GI disorders. One research group found that hEDS patients were more likely to have a functional GI disorder in the bowel (40% vs. 90%, $p< 0.0001$), esophagus (6% vs. 56%, $p< 0.0001$), anorectal (9% vs. 53%, $p< 0.0001$), and gastroduodenal (13% vs. 70%, $p< 0.0001$) regions of the GI tract when compared to healthy controls [14]. Other conditions reported within the hEDS population in addition to functional GI disorders include intestinal gastroesophageal disease (GERD), irritable bowel syndrome (IBS), functional constipation, gastroparesis, dysmotility, small intestinal bacterial overgrowth, food intolerances/allergies, vitamin D deficiency, and macronutrient intake imbalance [5,9]. One study even reported that that the risk of eating disorder development is higher among hEDS patients, which was theorized to stem from food intolerances and/or allergies [15]. The myriad of GI disorders and symptoms reported here well-illustrate the fact that people with hEDS or HDS often have increased GI symptoms and/or disorders.

Unfortunately, quality of life for those with hEDS or HDS and GI conditions is often poor. For instance, Lam and colleagues (2021) [14] assessed pain using the Patient Health Questionnaire-12 somatization score and found that hEDS patients have statistically significant medium to high somatic pain. A second study concluded that physical functioning, role limitations due to physical health, role limitation due to emotional health, level of energy/fatigue, social functioning, pain, and general health among 45 people with hEDS was significantly lower when compared to healthy adults

[16]. Another research team assessed quality of life among 603 people with hEDS and found statistically significant difference in physical functioning, bodily pain, general health, vitality, social functioning, emotional role, mental health, and physical role compared to healthy adults [14]. When considering quality of life and the GI manifestations of hEDS, it is important to note their potential interaction, that is the fact that dietary intake can not only affect quality of life, but quality of life can also impact dietary intake. For instance, joint pain and muscle weakness are common in hEDS and could be a limitation to accessing, preparing, and consuming food, resulting in poor dietary intake. Dietary intake, of course, is important for quality of life, impacting physical function and disability [17,18].

In support of the role hEDS and HSD play in affecting dietary intake, one of the more comprehensive studies of hEDS and HSD, conducted in 18 adults with medically diagnosed hEDS or HSD, found that carbohydrate intake was increased and protein intake was decreased compared to healthy controls. This same study found that pre-menopausal women with medically diagnosed hEDS or HSD, who had significant GI complications also had decreased protein intake and decreased Bone Mineral Density (BMD) when assessing left and right femoral BMD Z scores, spine BMD Z score, and right femoral BMD T score [19]. DiFrancisco-Donoghue and colleagues (2022) concluded that there is some evidence that there is a positive trend in protein intake and BMD, that participants in this study may be at risk for bone mineral abnormalities in the long term due to starting at a lower bone mineral baseline, and that vertebral fracture presence was significantly associated with trabecular bone scores. GI complications resulting in reduced protein intake long-term within the hEDS/HSD population may have lasting effects on bone health, physical function, and disability [17,18]. Thus, dietary protein should be a point of emphasis for researchers and clinicians involved with hEDS and HDS.

Vitamin D, another nutrient associated with bone and muscle health, also seems to be decreased in people with hEDS and HDS [20-22]. Only two studies to date have assessed vitamin D status in EDS patients altogether. One study was conducted in 22 people with vascular Ehlers-Danlos Syndrome (vEDS) and found that 14 of the 22 (63.6%) patients had low or critically low vitamin D levels. One person even had below threshold vitamin D levels despite dietary supplementation [23]. The other study was conducted in 72 infants less than 1 year of age whose parent(s) were accused of child abuse and neglect due to infantile bone fractures. Researchers found that 67 (93.1%) of the infants had clinical evidence of EDS or a family history of at least one parent having clinical symptoms of EDS. Of these 67 infants, 43 (64.2%) underwent plasma vitamin D testing. Twenty-seven infants (62.8%) were deficient (i.e, <20 ng/mL) in vitamin D and 11 (25.6%) were insufficient (i.e, 21-29 ng/mL). In addition, these researchers found that 16 of the mothers of the infants included in the study were deficient in vitamin D and showed signs of hEDS themselves [24]. It has been well established that vitamin D is essential for regulating calcium and phosphate metabolism and maintaining a healthy mineralized skeleton [25]. A vitamin D deficiency within the hEDS population from birth can impact development of bone and strength of the endoskeleton. In support of this, decreased bone mineral density and vertebral abnormalities appear to be common in hEDS and some researchers recommend newly diagnosed patients receive spine radiographs and bone mineral density assessments [26]. Do and colleagues (2021) [11] recommend a 5,000 IU/day supplement of vitamin D3 to hEDS patients [11]. Thus, the development of decreased bone mineral density and vertebral abnormalities observed in hEDS patients may be due to long-term vitamin D deficiency, but this demands more research. Regardless, those with or suspected of having hEDS or HDS should undergo 25-hydroxycholecalciferol testing to determine serum vitamin D levels and discuss supplementation with their healthcare provider.

Beyond these nutrient deficiencies, Zarate and colleagues (2010) [9] conducted a retrospective study of 129 people and reported that those with hEDS were more likely to experience reflux symptoms (56% vs. 30%, p= 0.0005) and abdominal bloating (62% vs. 46%, p= 0.05) than healthy controls. This research group also found that patients experiencing these symptoms were more likely to be female (86% vs. 65%, p= 0.008 [9]). In 2020, Zhou and colleagues conducted a retrospective review of 75 hEDS patients with gastrointestinal complaints. The researchers found that 26 (34.7%) of the patients tested positive for small intestinal bacterial overgrowth via glucose and lactulose breath testing [27], which can cause bloating and abdominal discomfort and is typically treated using antibiotics [28]. The treatment for these reflux, bloating, and abdominal discomfort symptoms should be focused on symptom improvement and prevention. Based on data extrapolated from studies in subjects with conditions that have similar symptoms to hEDS and HSD, dietary interventions such as eliminating foods the person has a sensitivity to and incorporating probiotic rich foods and/or prebiotic foods and/or supplements to the patient's diet may help with these symptoms [11]. More research is needed to determine the utility of these approaches in people with hEDS and HDS, and dietary guidance should be given by a registered dietician or other qualified professional.

Conclusions

Generally, information regarding hEDS and HSD, GI symptoms, and dietary approaches to treat these symptoms is sparse. The etiology of GI symptoms related to these syndromes is unclear, and few works have investigated dietary intake in people with hEDS and HSD. Nonetheless, it is clear that those with hEDS

and HSD are more likely to suffer from GI symptoms and that these symptoms negatively affect quality of life. Bloating, reflux, and abdominal discomfort are GI symptoms of hEDS and HSD and can potentially be managed using dietary approaches such as avoiding problematic foods and consuming more probiotics and/or prebiotics. However, these interventions have not been tested in this population, and dietary guidance should always be given by a professional. Limited evidence suggests that protein and vitamin D intakes are lower in those with hEDS and HSD, and these nutrients are well known for playing critical roles in the musculoskeletal system making them nutrients of interest for this population.

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