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Review

Nutritional Aspects of Ehlers–Danlos Syndrome: A Narrative Review of Available Evidence

Athanasios Gkoutzourelas [1], Arriana Gkouvi [1], Eleni C. Pardali [1], Penelope S. Papadopoulou [1], Dimitrios G. Goulis [2], Dimitrios P. Bogdanos [1] and Maria G. Grammatikopoulou [1,*]

[1] Immunonutrition and Clinical Nutrition Unit, Department of Rheumatology and Clinical Immunology, Medical School, University of Thessaly, Biopolis, GR-41110 Larissa, Greece; thanos_gkoutz@hotmail.com (A.G.); argkouvi@uth.gr (A.G.)

[2] Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Faculty of Health Sciences, Aristotle University of Thessaloniki, GR-56403 Thessaloniki, Greece

* Correspondence: mgrammat@uth.gr

Abstract

Ehlers–Danlos syndromes (EDS) comprise a heterogeneous group of connective-tissue disorders with multisystem manifestations that may adversely impact nutritional status. Nutritional concerns appear particularly relevant in hypermobile EDS (hEDS) and hypermobile spectrum disorders (HSD). The present review aims to synthesize evidence on nutritional status, dietary challenges, and nutritional management in EDS, with particular attention to hEDS and HSD, and identify evidence gaps regarding nutritional interventions. A comprehensive search was conducted in PubMed/MEDLINE and Scopus until 6 September 2026. Relevant publications were selected through a topic-driven approach, prioritizing primary studies involving EDS/hEDS/HSD populations and incorporating evidence from related conditions, when direct evidence was limited. The literature indicates that nutritional vulnerability is heterogeneous and cannot be inferred from body mass index alone. Dietary inadequacies, particularly regarding vitamin D, fiber, Potassium, Iron, Magnesium, Copper and selected B vitamins have been reported, although biochemical confirmation of definite deficiencies remains limited for most micronutrients. Restrictive eating pertains in selected hEDS/HSD cohorts, while objective gastrointestinal dysmotility appears less consistently demonstrated than symptom burden. Evidence supporting specific EDS diets, elimination diets or dietary supplements remains insufficient to draw conclusions for recommendations. Nutritional management should emphasize on individualized assessment based on the ABCDE framework, in order to guide the management of identifiable gastrointestinal and autonomic conditions, optimize oral intake, and offer efficient dietary interventions. Enteral and parenteral nutrition should be reserved for clearly established indications, following multidisciplinary assessment. Prospective trials, biochemical characterization, and pediatric studies remain research priorities.

Keywords: immunonutrition; hypermobility; connective-tissue disorder; hypermobile spectrum disorder; eating disorders; MCAS; POTS; mast-cell activation; low-histamine diet; FODMAP; gluten-free

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Academic Editor: Nagaraja Haleagrahara

Received: 18 October 2026
Revised: 18 November 2026
Accepted: 20 November 2026
Published: 21 November 2026

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1. Introduction

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective-tissue disorders (CTD) characterized by variable combinations of joint hypermobility, skin hyperextensibility, and tissue fragility, arising primarily from qualitative or quantitative

abnormalities in collagen synthesis, processing, or structural organization [1]. Their molecular basis extends beyond fibrillar collagen structure itself to defects in collagen processing, extracellular-matrix organization, and related biosynthetic pathways. The 2017 International Classification of the Ehlers–Danlos Syndromes recognized 13 clinically and molecularly distinct EDS types and established diagnostic criteria for each one [1]. Molecular confirmation is expected for all types except for hypermobile EDS (hEDS), for which no single diagnostic genetic marker is currently available [1,2]. Biallelic variants in the adipocyte enhancer-binding protein 1 (*AEBP1*) gene were subsequently associated with a classical-like phenotype, described as classical-like EDS type 2 (clEDS2) and proposed as the 14th EDS type [3,4].

EDS has an overall estimated prevalence of 1 in every 2500–5000 births, though underrecognition and underdiagnosis likely masks the true figure, with hEDS accounting for 80–90% of the total identified cases [5,6]. A more recent study revealed that 1 in every 500 Welsh people has a diagnosis of either EDS, or joint hypermobility syndrome [7]. On the other hand, Zloof and associates identified 4686 adolescents with HSD/hEDS among a total of 1627.345 Israeli adolescents assessed, reaching a prevalence of 0.29% [8]. Regarding hEDS, the reported prevalence is most likely underestimated, given that diagnoses are often missed [9]. On the other hand, the term "hypermobile spectrum disorder" (HSD) describes symptomatic joint hypermobility that cannot be explained better by another condition and does not meet the criteria for hEDS, or another heritable CTD. Therefore, HSD does not consist of an EDS subtype, even though these two entities—hEDS and HSD—are commonly considered together in clinical studies, due to their overlapping manifestations and common management requirements [2,10]. This distinction is particularly important since the literature—which is derived predominantly from adults with hEDS/HSD—cannot necessarily be generalized to genetically confirmed rare EDS types.

Nutrition has received increasing attention in hEDS/HSD because gastrointestinal (GI) symptoms, disorders of gut–brain interaction (DGBI), autonomic dysfunction, chronic pain and functional limitations may all interfere with adequacy in the dietary intake and nutritional status [11–15]. Recent studies have identified substantial dietary restriction, positive screening for Avoidant/Restrictive Food Intake Disorder (ARFID), inadequate intake of several micronutrients and use of nutritional support in subsets of patients with hEDS/HSD [14–19]. However, GI symptoms and dietary restriction do not necessarily indicate malabsorption, organic GI disease or objective intestinal dysmotility, making nutritional assessment in this population a particularly complex task.

A recent meta-analysis involving 17,455 individuals with hEDS/HSD estimated that 65.3% of the population experience at least one chronic GI symptom [20]. Individual studies applying the Rome IV criteria have reported substantially greater rates, with up to 98% of the patients meeting the criteria for one or more DGBI, compared to the 47% reported by healthy controls [11]. Taken together, these findings establish a substantial GI symptom burden in hEDS/HSD, while also demonstrating marked variation according to study population, diagnostic definitions, and clinical setting. They do not, however, indicate that the reported symptoms arise from a single structural or mechanistic abnormality.

At the same time, interest in the optimal EDS diet and effective connective-tissue dietary supplements has grown faster than the supporting clinical evidence. Patients frequently experiment with gluten-free, dairy-free, low-fermentable-carbohydrate, low-histamine, and other elimination diets, often in the absence of formal dietetic guidance [17]. This pattern is consistent with broader evidence that patients with hEDS/HSD, facing limited in-person clinical resources, increasingly turn to social media and online communities for disease-related information and peer support; a source that, although valuable, also carries the risk of misinformation [17,21]. Meanwhile, tertiary services report patients progressing

from oral restriction to tube feeding, intravenous (IV) fluids, or parenteral nutrition (PN) despite limited objective evidence of intestinal failure [22]. The clinical challenge is therefore twofold: genuine nutritional compromise must be identified and treated, while unnecessary dietary restriction, supplementation and invasive nutrition should be avoided.

Despite growing recognition of these issues, the nutritional aspects of EDS remain insufficiently described and the lack of an EDS-specific nutritional management framework is evident. The purpose of this narrative review was to critically synthesize the nutritional aspects of EDS across four levels of evidence: findings generated directly in EDS/hEDS/HSD populations; evidence derived from associated conditions such as DGBI, gastroparesis, postural orthostatic tachycardia syndrome (POTS), or Mast-Cell Activation Syndrome (MCAS); general clinical nutrition principles; and biologically plausible, but yet untested hypotheses. Particular attention is given to the mechanisms linking connective-tissue dysfunction to GI impairment and nutritional adequacy, clinical challenges including ARFID, POTS, and MCAS, micronutrient deficiencies, available dietary and artificial nutrition interventions, and to the particularities of the pediatric population, with the ultimate goal of identifying knowledge gaps and proposing directions for future research.

2. Methods

2.1. Search Strategy

As this is a narrative review, no prospective protocol was registered, and no formal assessment of the quality of included studies was undertaken. A literature search was conducted in the PubMed/MEDLINE and Scopus databases, until 6 September 2026. Searches were conducted by At.G., and screening was performed independently by At.G., Ar.G., and E.C.P., with disagreements resolved by discussion with more senior authors.

Rather than employing a single predefined search string, searches were progressively refined according to the thematic areas covered by the review. Search terms related to Ehlers–Danlos syndromes (e.g., "Ehlers–Danlos syndrome", "hypermobile Ehlers–Danlos syndrome", and "hypermobility spectrum disorder") were combined, as appropriate, with terms addressing nutritional status, dietary intake, malnutrition, micronutrient deficiencies, body composition, eating disorders, dietary interventions, and nutritional support. Additional topic-specific searches focused on GI manifestations, DGBI, gastroparesis, POTS, and MCAS. Reference lists of relevant reviews, clinical practice updates, and consensus statements were also screened, in order to identify additional publications.

English-language publications were considered eligible if they addressed nutritional status, dietary challenges, dietary intake, or dietary management in individuals with EDS, hEDS, or HSD. Publications involving related conditions, including DGBI, gastroparesis, POTS, and MCAS, were also considered when they addressed nutritional questions relevant to the review. Non-English publications and those without relevant nutritional or dietary content were excluded. The restriction to English-language sources may have excluded the relevant non-English literature, particularly French- and Italian-language studies, given the observed EDS research interest in these countries; this is acknowledged as a limitation.

Priority was given to primary studies directly involving EDS/hEDS/HSD populations, particularly those reporting quantitative nutritional outcomes or evaluating nutritional interventions. Relevant meta-analyses, narrative reviews, clinical practice guidelines, and consensus statements were used to contextualize the available evidence. Greater emphasis was given on studies published after the release of the 2017 international EDS classification [1], with earlier landmark studies retained, where still relevant.

2.2. Construction of Figures

The figures presented herein have been created using BioRender software (web version) under active Publication License (Science Suite Inc., Toronto, ON, Canada) [23]. Additionally, the use of Canva (web version, Canva Pty Ltd., Sydney, Australia) software was sought, with individual graphical elements employed in accordance with the Canva Pro licensing terms [24].

3. Nutritional Risk and Dietary Adequacy

3.1. Determinants of Nutritional Risk

Nutritional vulnerability in EDS is multifactorial and is likely more relevant in hEDS/HSD, from which most of the nutritional evidence is derived. This hypothesis is reflected by the multisystemic nature of the underlying connective-tissue defect and its direct and indirect effects on GI function, autonomic regulation, tissue integrity, and physical capacity [10–13,25]. Table 1 summarizes the 13 EDS types included in the 2017 international classification of EDS, as well as the *AEBP1*-related classical-like EDS type 2, which was proposed subsequently, with the respective known genetic mutations/proteins involved, as well as key the clinical features, GI and visceral manifestations of each type. Of note, nutritional vulnerability in this population should not be equated automatically with malabsorption.

Table 1. EDS types: genetics, key clinical features, and GI or visceral manifestations.

EDS Type	Inheritance	Gene(s)/Protein	Key Clinical/Systemic Features	GI and Visceral Manifestations
Classical (cEDS) [9]	AD	*COL5A1*, *COL5A2* (>90%); rarely *COL1A1*	Skin hyperextensibility, atrophic scarring, generalized joint hypermobility, easy bruising	Recurrent abdominal hernias (umbilical, inguinal) listed as a minor criterion; rectal/pelvic organ prolapse reported in case series; no specific mechanistic GI finding established.
Classical-like (clEDS-TNXB) [9]	AR	*TNXB* (complete absence of tenascin-X)	Velvety skin without atrophic scarring, generalized joint hypermobility, easy bruising	Vaginal/uterine/rectal prolapse explicitly listed as a minor criterion.
Classical-like type 2 (clEDS2) [3,26]	AR	*AEBP1* (proposed 14th type, post-2017)	Classical-like phenotype; skin fragility	No subtype-specific GI association has been established in the available literature.
Cardiac-valvular (cvEDS) [27]	AR	*COL1A2* (complete absence of pro-α2(I) chains)	Severe progressive valvular heart disease, skin involvement, joint hypermobility	No subtype-specific GI association has been established in the available literature.
Vascular (vEDS) [28]	AD	*COL3A1* (main); rarely arginine-to-cysteine *COL1A1* substitutions	Arterial and organ fragility—the most severe subtype	Spontaneous sigmoid colon perforation (absence of diverticular disease) is a MAJOR diagnostic criterion. Bowel perforation is a major vEDS complication; recurrent colonic perforation reported in roughly one-third of affected individuals.
Hypermobile (hEDS) [10]	AD (presumed)	Unknown	Generalized joint hypermobility, chronic pain, fatigue—80–90% of all EDS cases	The EDS type for which the greatest volume of GI-related evidence is currently available; high rates of DGBI and symptoms including constipation, dyspepsia, dysmotility, ARFID, gastroparesis, nausea and reflux have been reported in hEDS/HSD cohorts. No collagen-related mechanism in the GI wall has been established.

Table 1. *Cont.*

EDS Type	Inheritance	Gene(s)/Protein	Key Clinical/Systemic Features	GI and Visceral Manifestations
Arthrochalasia (aEDS) [29]	AD	*COL1A1*, *COL1A2* (exon 6 loss)	Congenital bilateral hip dislocation, severe joint hypermobility	No subtype-specific GI association has been established in the available literature.
Dermatosparaxis (dEDS) [30,31]	AR	*ADAMTS2*	Extreme skin fragility, characteristic craniofacial features	Visceral fragility complications explicitly listed as a minor criterion: bladder rupture, diaphragmatic rupture, rectal prolapse.
Kyphoscoliotic (kEDS-*PLOD1*/-*FKBP14*) [32,33]	AR	*PLOD1* (LH1); *FKBP14*	Congenital muscle hypotonia, progressive kyphoscoliosis	Umbilical/inguinal hernia listed as a minor criterion; reduced life expectancy mainly driven by cardiopulmonary rather than GI involvement.
Brittle Cornea Syndrome (BCS) [34,35]	AR	*ZNF469*, *PRDM5*	Thin cornea, keratoconus/keratoglobus	No subtype-specific GI association has been established in the available literature.
Spondylodysplastic (spEDS) [36–38]	AR	*B4GALT7*, *B3GALT6*, *SLC39A13*	Short stature, muscle hypotonia, skeletal abnormalities	Minimal specific GI documentation; hypotonia could theoretically affect motility, but no explicit mention in diagnostic criteria.
Musculocontractural (mcEDS-*CHST14*/-DSE) [39]	AR	*CHST14* (*D4ST1*); DSE	Congenital multiple contractures, characteristic craniofacial features	Explicit GI/genitourinary minor criteria: chronic constipation, colonic diverticula, pneumothorax/pneumohemothorax, nephrolithiasis/cystolithiasis, cryptorchidism.
Myopathic (mEDS) [1]	AD or AR	*COL12A1*	Congenital muscle hypotonia/atrophy, improving with age	No subtype-specific GI association has been established in the available literature.
Periodontal (pEDS) [40]	AD	C1R, C1S (complement pathway)	Severe early-onset periodontitis, lack of attached gingiva	Hernias listed as a minor criterion; otherwise predominantly orofacial findings.

AD: autosomal dominant; AR: autosomal recessive; ARFID: Avoidant/Restrictive Food Intake Disorder; C1R: Complement C1r; C1S: Complement component 1s; DGBI: disorders of gut–brain interaction; EDS: Ehlers–Danlos syndrome; GI: Gastrointestinal; LH1: Lysyl Hydroxylase 1.

GI symptoms such as early satiety, postprandial fullness, nausea, abdominal pain, dysphagia, difficulty in breathing, choking, reflux, constipation, and diarrhea may collectively reduce meal size and frequency, or constrain dietary variety. DGBI and organic GI disease often coexist, but symptom intensity alone does not reliably identify the underlying mechanism, or the degree of nutritional compromise [11,13,41,42].

Nutritional risk may also arise independently of GI dysfunction. Chronic pain, joint instability, fatigue, impaired hand function, and orthostatic intolerance often interfere with shopping, cooking, remaining in an upright position during food preparation, chewing, sitting for meal consumption, as well as with self-feeding. Superimposed feeding-related anxiety, restrictive eating patterns, and elevated ARFID risk may further narrow the range of tolerated foods, potentially compromising dietary adequacy, even in the absence of clinically apparent malnutrition. Financial limitations, dependence on carers, and reduced access to clinicians or dietitians may compound these barriers [17,22]. For these reasons, evaluation of the practical process of obtaining and eating food should be incorporated in the nutritional assessment model applied in these patients.

Importantly, nutritional risk cannot be inferred from body weight alone. Topan [14] revealed that only 5.2% of patients are in fact, underweight, whereas 46.4% are either over-

weight or obese, despite the observed low estimated adequacy in the energy intake in a substantial number of patients. This finding suggests that body mass index (BMI) alone is an inadequate and crude screening measure for assessing nutritional risk, as it fails to identify loss of muscle mass, poor dietary quality and intake, or micronutrient deficiencies. This pattern of apparently normal, or even elevated BMI values coexisting with functional or biochemical compromise is in agreement with respective findings in chronic rheumatologic disease [43–47]. Malnutrition and disease-related sarcopenia are increasingly recognized in rheumatoid arthritis (RA) and other systemic rheumatic conditions, where Global Leadership Initiative on Malnutrition (GLIM)-based prevalence estimates substantially exceed what BMI alone would predict [44,46,47]. While EDS is not an inflammatory disease per se, the shared features of chronic pain, fatigue, reduced mobility, and complex multisystem involvement suggest that comparable mechanisms of undernutrition risk may operate, even in the absence of active inflammation, a hypothesis that remains untested directly in EDS.

3.2. Dietary Intake and Adequacy: Direct Evidence

Direct evidence on the dietary intake of people with EDS remains sparse and almost entirely limited to hEDS/HSD. Table 2 details all published research assessing nutritional status and dietary intake among patients with EDS. An early study [48] revealed that patients with hEDS/HSD tend to consume less protein and more carbohydrate in their diets, while exhibiting lower bone mineral density (BMD) compared to healthy controls [48].

Table 2. Studies assessing nutritional status, dietary intake, and eating behaviours in EDS/HSD.

First Author	Country; Study Design	Sample	Nutritional Assessment Components	Key Findings	Key Limitations
Baeza-Velasco [49]	Spain; cross-sectional online survey, path analysis	N = 121 women with self-reported EDS	GI issues (PAGI-SYM), food allergies, SSAS, oral pain (OHIP-49), painful/fearful eating, eating avoidance and restriction, body satisfaction (BIQ), and BMI	Food allergies were reported by 51.2% of participants, 21.5% had obesity, 15.7% reported a history of AN, and 12.4% of BN. GI symptoms were associated with painful, fearful and avoidant eating.	Self-reported EDS; women only; potential selection bias.
Baeza-Velasco [25]	Spain; cross-sectional case–control	N = 66 women with EDS and N = 39 healthy controls	GI symptoms (heartburn/regurgitations, nausea/vomiting, early satiety, bloating, abdominal pain, dysphagia), food allergies/intolerances, disordered eating, history of ED, and BMI	EDS group reported more GI symptoms and disordered eating, and lower BMI; restricted eating was related to GI symptoms, food allergies/intolerances, and dysphagia, whereas uncontrolled eating was also associated with GI issues. BMI was related to GI symptoms and food allergies/intolerances.	Small, women-only sample; self-reported diagnosis and BMI.
DiFrancisco-Donoghue [48]	USA; observational matched case–control study	N = 18 women with hEDS/HSD (6 hEDS, 12 HSD); N = 18 age-/BMI-matched healthy women	Dietary intake (3-day food diary), GSRS, RMR, body composition and BMD (DXA), handgrip strength	Women with hEDS/HSD reported lower protein and higher carbohydrate intake; lower BMD z-scores. All women with hEDS/HSD reported GI symptoms. No between-group differences were observed in the caloric intake, body composition, or grip strength.	Very small, women-only sample; short dietary record.

Table 2. *Cont.*

First Author	Country; Study Design	Sample	Nutritional Assessment Components	Key Findings	Key Limitations
Topan [17]	UK; cross-sectional questionnaire survey	N = 680 patients with hEDS/HSD (95% women); patient organization and tertiary GI clinics	Dietary behaviors, nutritional support, DGBI (Rome IV), GI symptoms, ARFID, POTS, MCAS	62.1% altered their diet; 62.3% skipped meals. Dietary modification was associated with reflux symptoms, functional dyspepsia, self-reported MCAS, and positive screening for ARFID, particularly symptoms pertaining to fear of eating and low food interest.	Self-report and recruitment bias; ARFID screening, not diagnosis.
Topan [14]	UK; cross-sectional FFQ and cluster analysis	N = 425 patients with hEDS/HSD (96% women), recruited from patient organization and tertiary GI clinics	FFQ, BMI, DGBI, GI symptoms, ARFID, and use of nutrition support	Nearly half (46.4%) of the patients were overweight or obese. Dietary intake was high in protein and fat, but low in energy, certain B vitamins and vitamin D; only 24.7% met fiber intake recommendations. Four dietary patterns were identified; low-intake group had greatest estimated inadequacy and higher ARFID scores.	FFQ estimation bias; no biochemical deficiency confirmation.
Sood [50]	USA; retrospective single-center cohort	N = 435 symptomatic children/young adults with clinically diagnosed hEDS/JHS, aged 5–28 years, attending tertiary GI clinics	GI symptoms, weight loss, dysphagia/reflux, dyspepsia/gastroparesis symptoms, constipation, endoscopy, gastric emptying, and motility testing	Constipation (61%), dysphagia (32%), dyspepsia/gastroparesis symptoms (25%), EoE (21%), and CD (4%) were common. EoE was more common in those with dysphagia.	Retrospective, symptomatic tertiary-care cohort; no asymptomatic comparator; limited generalizability.

AN: anorexia nervosa; ARFID: avoidant restrictive food intake disorder; BIQ: Body Image Questionnaire; BMD: Bone mineral density; BMI: body mass index; BN: bulimia nervosa; CD: celiac disease; DGBI: Disorders of gut–brain interaction; DXA: dual-energy x-ray absorptiometry; ED: eating disorder; EDS: Ehlers–Danlos syndrome; JHS: joint hypermobility syndrome; EoE: eosinophilic esophagitis; FFQ: food frequency questionnaire; GI: gastrointestinal; GSRS: Gastrointestinal Symptom Rating Scale; hEDS: hypermobile Ehlers–Danlos syndrome; HSD: hypermobility spectrum disorder; MCAS: mast-cell activation syndrome; OHIP-49: Oral Health Impact Profile; PAGI-SYM: Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index; POTS: postural tachycardia syndrome; RMR: Resting metabolic rate; SSAS: Somato-Sensory Amplification Scale; TFEQ: Three-Factor Eating Questionnaire; UK: United Kingdom.

More recently, Topan [14] conducted the largest assessment of nutrient intake in hEDS/HSD using a validated 169-item food-frequency questionnaire (FFQ) compared against the United Kingdom (UK) dietary reference values (DRV) [14]. Only 33.4% of the participants met the estimated average requirement (EAR) for energy, and fiber intake was low (24.7% meeting the reference value), while the recommended saturated fatty acid (SFA) intake was exceeded by most (88.0%) participants. Dietary adequacy was also low for Potassium (40.2%), Iron (45.6%), Magnesium (57.4%), Copper (58.8%), and Selenium (36.0%). Dietary vitamin D intake was strikingly low (4.5% of the DRV), and B-complex adequacy was somewhat lower than recommended regarding folate (71.5%), riboflavin (77.4%), and niacin (69.6%) intake. In contrast, 87.3% of the patients met the recommended protein intake and more than 90% met reference values for vitamins B12 and C [14]. This

heterogeneous pattern of selective micronutrient inadequacy rather than uniform deficiency, argues against a single "EDS diet" and highlights the need for conducting individualized dietary assessments. In the same cohort, four empirically derived dietary patterns were identified, namely the "low-food intake", the "vegetarian/health-conscious" one, the "low-residue" and the "refined/highly processed" foods pattern [14]. The low-food intake pattern ($n = 149$) was associated with the greatest nutritional vulnerability, with only 4.7% of the patients meeting energy requirements and 0.7% meeting the fiber reference value, alongside more food-related and autonomic symptoms, the highest rate of positive ARFID screening, and the greatest use of nutritional support. The vegetarian/health-conscious pattern ($n = 120$) was related to the most favorable fiber and micronutrient intake, whereas on the other hand, the refined/highly processed foods pattern ($n = 121$) was associated with greater BMI values (overweight), more severe indigestion, and greater GI-specific anxiety. As for the low residue pattern ($n = 35$), it was disproportionately drawn from tertiary clinics. Taken together, these findings suggest that inadequate dietary intake in hEDS/HSD may be more pronounced in identifiable subgroups, particularly those with globally low intake, or ARFID-related features, rather than occurring uniformly across all patients. Furthermore, an hEDS/HSD diagnosis alone does not automatically identify individuals at nutritional risk [14]. These findings should be interpreted cautiously because dietary intake and BMI were self-reported, patients receiving nutritional support were excluded, no contemporaneous control group was included, and the use of UK-specific DRV limit generalizability. Furthermore, the cross-sectional design adopted precludes causal inferences regarding the relationship between dietary patterns and symptoms.

3.3. Nutritional Screening and Assessment

General nutritional screening and diagnostic frameworks have been developed and validated in populations outside EDS/HSD, and their performance in this population remains unestablished. Consequently, their applicability should be considered in light of the clinical heterogeneity of EDS/HSD, and disease-specific validation studies are required. The GLIM criteria provide a framework for diagnosing malnutrition, on the basis of at least one phenotypic (weight loss, low BMI, reduced muscle mass) and one etiologic criterion (reduced intake/assimilation, or disease burden) [16]. Other established tools, such as the Mini Nutritional Assessment (MNA), the Malnutrition Universal Screening Tool (MUST), the Patient-generated Subjective Global Assessment (PG-SGA), and the Nutritional Risk Screening (NRS-2002) support screening across different settings [51–53]. In hEDS/HSD, reduced dietary intake should be documented rather than inferred from GI symptoms, and systemic inflammation should not be presumed given the non-inflammatory nature of the underlying connective-tissue defect. Likewise, body weight history, muscle mass, dietary adequacy and food variety should also be considered. Given that nutritional compromise may occur despite normal or elevated BMI, systematic assessment may allow nutritional problems to be identified before overt malnutrition develops. Table 3 presents a proposed ABCDE-based approach to a comprehensive nutritional assessment, adapted from general clinical nutrition principles to address relevant clinical and functional challenges in EDS/HSD. This framework is intended as a practical organizational aid rather than a validated EDS/HSD-specific assessment instrument.

Table 3. ABCDE nutritional assessment framework for patients with EDS/HSD.

Assessment Domain	Assessment
Anthropometric	Body weight history, weight loss, low BMI, reduced muscle mass, or growth/weight trajectory changes, normal/elevated BMI despite compromise.

Table 3. *Cont.*

Assessment Domain	Assessment
Biochemical	Nutritional deficiencies, e.g., micronutrient deficiencies or abnormal nutrition-related blood markers. Disease burden/inflammation. Test for SIMD.
Clinical	GI symptoms: early satiety, postprandial fullness, nausea, abdominal pain, dysphagia, reflux, constipation, diarrhea; plus DGBI, organic GI disease, chronic pain, joint instability, fatigue, impaired hand function, orthostatic intolerance. Reduced muscle mass.
Dietary	Reduced meal size, meal frequency, dietary variety, assimilation, restrictive eating patterns, narrowed tolerated foods, ARFID risk, or other ED.
Environmental/functional	Difficulty shopping, cooking, staying upright during food preparation, chewing, sitting for meals, self-feeding; financial limitations, dependence on carers, reduced access to clinicians/dietitians. Systematic assessment before overt malnutrition develops.

ARFID: avoidant restrictive food intake disorder; BMI: body mass index; DGBI: Disorders of gut–brain interaction; ED: eating disorder; EDS: Ehlers–Danlos syndrome; GI: gastrointestinal; HSD: hypermobility spectrum disorder; SIMD: small intestinal microbial dysbiosis.

4. Gastrointestinal Drivers of Nutritional Risk

4.1. Symptom Burden and Disorders of Gut–Brain Interaction (DGBI)

GI symptoms are among the most consistently reported extra-articular manifestations in hEDS/HSD, with prevalence estimates that substantially exceed those observed in the general population [20]. Lam [11] assessed the Rome IV criteria to individuals with hEDS/HSD and age- and sex-matched controls, revealing that 98% of the patients met the criteria for at least one DGBI. Moreover, most (84%) of the affected patients met the criteria for DGBI in two or more anatomical regions, indicating a pattern of diffuse, multi-segment gut dysfunction rather than an isolated single-organ disorder.

The broader evidence was synthesized in a systematic review and meta-analysis including 17,455 patients with hEDS/HSD [20]. The pooled prevalence of at least one chronic GI symptom was 65.3%, while the pooled prevalence of DGBI was 44.2%. Additionally, among case–control studies, hEDS/HSD was associated with greater odds of chronic GI symptoms [odds ratio (OR): 4.17; 95% CI: 3.02–5.77]. The odds of exhibiting DGBI were similarly increased (OR: 4.97; 95% CI: 3.1–8.0). These pooled estimates support a clinically important association, but require cautious interpretation since heterogeneity exceeded 94% in the principal analyses, reflecting differences in diagnostic criteria, study populations, symptom definitions, and control groups [20]. The findings are consistent with a 20-year Mayo Clinic retrospective cohort study, in which 56% of patients with EDS reported clinically significant GI manifestations [15]. Most commonly presenting manifestations included abdominal pain, nausea, constipation, and heartburn/gastroesophageal reflux disease (GERD), with irritable bowel syndrome (IBS) representing the most frequent specific diagnosis [15]. In a recent propensity-matched health-record study (59,128 patients with EDS and 59,128 controls) EDS was similarly associated with a greater recorded prevalence of GI comorbidities, including GERD and IBS [54]. This evidence supports a substantial GI symptom burden, although differences in diagnostic definitions, patient selection and study design limit direct comparisons.

In recognition of the breadth and clinical significance of GI symptoms in patients with EDS, the American Gastroenterological Association (AGA) issued a 2025 Clinical Practice Update, specifically addressing GI manifestations and autonomic/immune dysfunction in hEDS [55]. According to this clinical practice update, a standard DGBI diagnostic approach is recommended, supplemented by targeted testing for celiac disease, pelvic-floor dysfunction, gastric motor disorders, POTS, and MCAS, when clinically indicated [55]. Notably, the update explicitly cautions that universal testing for POTS or MCAS in all

patients with hEDS/HSD is not supported by current evidence, and that while theoretical mechanistic explanations linking these conditions exist, experimental evidence remains limited and evolving [55]. This multi-system testing strategy reflects growing recognition that GI symptoms in hEDS/HSD rarely occur in isolation, but are frequently intertwined with autonomic and immune dysregulation, even though rigorous mechanistic evidence connecting them remains limited.

4.2. Collagen Biology and the Gastrointestinal Tract

The GI tract contains an extensive extracellular matrix, including collagen, which contributes to the structural integrity and mechanical properties of the intestinal wall. This provides a biological rationale for investigating whether connective-tissue abnormalities in EDS contribute to gastrointestinal manifestations. However, the extent to which such abnormalities directly influence GI motility, visceral sensation, or other functional disturbances remains uncertain and may differ substantially between EDS subtypes. In the human intestine, type I collagen predominates (~68% of total collagen), followed by type III (~20%) and type V (~12%), with type V localized predominantly to the submucosa [56]. Fibrillar collagens type I and III form the principal structural scaffold of the submucosa, muscularis propria, and serosa, conferring tensile strength and structural integrity to the bowel wall. Type V collagen regulates the diameter and lateral organization of these fibrils, while type IV collagen is a minor but characteristic constituent of the basement membrane underlying the mucosal epithelium [56]. Of note, these proportionate data derive from macroscopically normal tissue resected from patients with Crohn's disease, rather than healthy controls, indicating a limitation of the available histological literature on this topic [56].

The clearest and best-established example of a direct mechanistic link between a collagen defect and gastrointestinal pathology is vascular EDS (vEDS), caused by pathogenic variants in *COL3A1*. In this EDS subtype, defective type III collagen predisposes to spontaneous bowel and arterial rupture. This complication accounts for a well-documented, life-threatening condition, with recurrent colonic perforation reported in roughly a third of affected individuals [57].

The situation is considerably less certain in hEDS. To date, no causative molecular defect has been established for hEDS. Although alterations in connective-tissue mechanical properties have been described, their proposed contribution to intestinal motility, tone, sensation, or permeability has not been established through direct mechanistic studies in hEDS/HSD [55]. This distinction carries important clinical implications suggesting that mechanistic extrapolation from vEDS to hEDS/HSD should be made with caution. Thus, clinicians should avoid conveying a degree of mechanistic certainty regarding hEDS/HSD that the current evidence does not support.

4.3. Dysmotility and Gastroparesis

Evidence regarding objective GI dysmotility in hEDS/HSD is conflicting. In the Mayo Clinic cohort, objective motility testing among symptomatic patients demonstrated abnormal gastric emptying, colonic transit and rectal evacuation [15]. A subsequent tertiary-care study similarly reported GI dysmotility in 76.2% of patients, with gastroparesis identified in 42.8%. POTS emerged as the strongest independent predictor of dysmotility (OR: 5.74) [58]. However, these findings arise from selected referral populations and should not be interpreted as estimates of dysmotility prevalence in the broader hEDS/HSD population.

More recent comparative evidence, however, has challenged the assumption that objective GI dysmotility is consistently more prevalent in patients with hEDS/HSD than in symptomatic individuals without these diagnoses. Sweerts [59] compared patients with hEDS/HSD to controls with GI symptoms, undergoing antroduodenal manometry and

failed to find differences in overall antroduodenal dysmotility or delayed gastric emptying between groups. Enteric dysmotility was, in fact, less common among patients with HSD/hEDS (13% vs. 34%) [59]. The authors suggested that delayed gastric emptying, rather than enteric neuropathy or myopathy, appears more clinically relevant to the GI symptoms in this population, although the report was brief and should be interpreted alongside the limitations of the larger retrospective studies [15,58,59].

Correspondence arising from this study further highlighted a notable discordance between objective motility findings and the use of artificial nutrition in hEDS/HSD [60]. This observation raises the possibility that factors beyond demonstrable enteric neuromuscular dysfunction, including food-related fear, restrictive eating, visceral hypersensitivity, and symptoms associated with dysautonomia, may contribute to feeding difficulties and decisions regarding the provision of nutritional support. However, the relative contribution of these factors has not been established [60].

Small intestinal microbial dysbiosis (SIMD) has also been investigated in patients with HSD and GI symptoms, with reported associations involving older age, previous abdominal surgery, and delayed gastric emptying [61]. Preliminary findings have additionally described small intestinal bacterial and fungal overgrowth (SIBO) in patients with EDS [62]. However, the available evidence does not establish whether these microbial alterations are directly related to the underlying CTD, secondary to GI dysfunction, or attributable to other clinical factors. As a result, their causal significance and implications for nutritional management in EDS/HSD remain uncertain.

Taken together, the available evidence indicates that objectively documented GI dysmotility occurs in some patients with hEDS/HSD, although its frequency and relationship with comorbid POTS remain incompletely characterized. Nevertheless, the data do not support the claim that dysmotility is a universal, or defining feature of the syndrome. Larger, prospective, standardized studies are required before enteric dysmotility can be considered an intrinsic hallmark of hEDS/HSD, rather than a comorbid, or confounded finding.

Gastroparesis and other motility disorders should not be diagnosed on the basis of symptoms alone; standardized objective testing protocols should be followed. Such protocols are outlined in the American College of Gastroenterology (ACG) clinical guideline on gastroparesis [63]. Dietary management strategies (including small, frequent meals, reduced particle size, adjustment of dietary fat and fiber content and use of liquid or blenderized nutrient sources) are extrapolated from general gastroparesis management guidelines, as no hEDS/HSD-specific dietary trials exist to date. Even within the broader gastroparesis literature from which these recommendations derive, current practice is itself acknowledged to rely on extrapolated rather than disease-specific evidence [64]. Fiber should be introduced cautiously, considering the frequent coexistence of bloating and abdominal pain in this population. For evacuation disorders, pelvic-floor physical therapy represents a reasonable adjunct, consistent with the high prevalence (60%) of abnormal rectal evacuation [15]. Figure 1 summarizes commonly reported GI symptoms in hEDS/HSD.

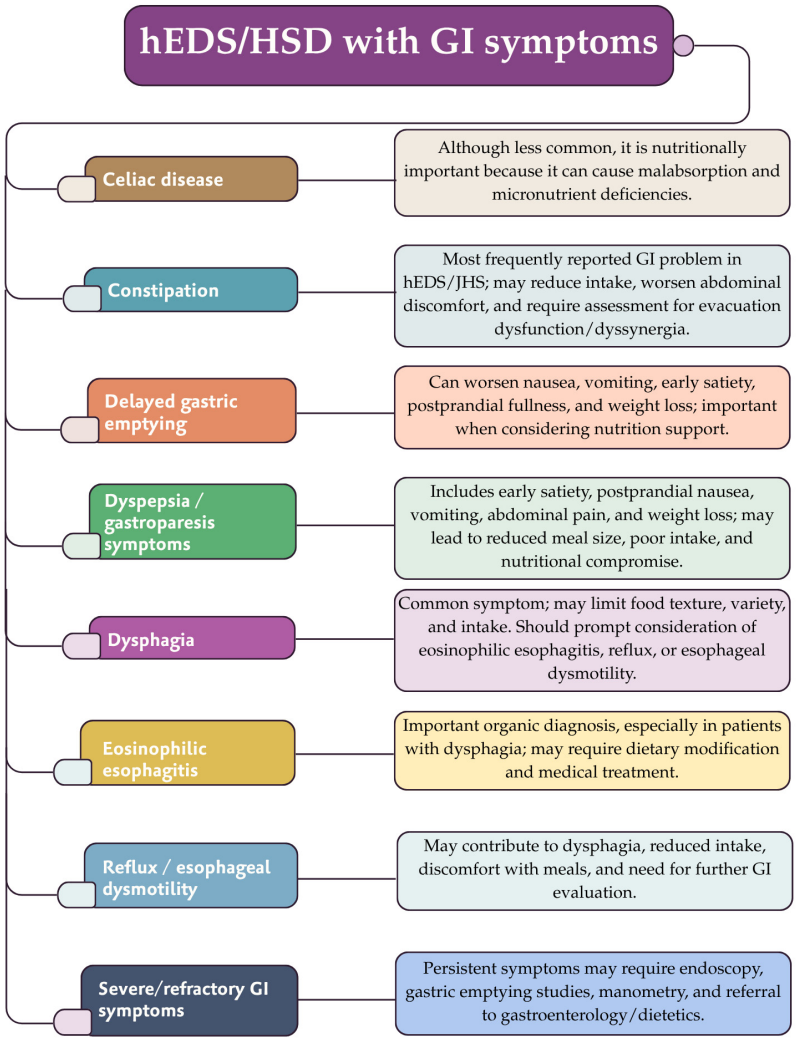


Figure 1. Common GI problems in hEDS/HSD. GI: gastrointestinal; hEDS: hypermobile Ehlers–Danlos syndromes; HSD: hypermobile spectrum disorders; JHS: Joint Hypermobility Syndrome.

5. Condition-Specific Nutritional Challenges

5.1. Restrictive Eating, Disordered Eating and ARFID

Food-related symptoms may initiate a cycle of avoidance, in which patients reduce meal size or restrict foods to prevent pain, nausea, reflux or presyncope, progressively narrowing dietary variety. This process can coexist with DGBI, organic disease, neurodevelopmental sensory differences, or even a formal eating disorder. In the Topan et al. study, 37.9% of the CANDI-hEDS cohort screened positive for ARFID [17]. Altered diet was associated with low interest in eating, GERD, functional dyspepsia, and self-reported MCAS, and the fear-of-aversive-consequences domain was the strongest predictor of nutrition-support use (OR: 4.97; 95% CI: 2.09–11.8) [17]. Compared to healthy controls, a greater prevalence of GI symptoms, food allergy/intolerance reports, disordered eating, and lower BMI are recorded among patients with EDS [25]. Similarly, among adults with CTD, 18.5% screened positive for ARFID symptoms and 50.2% for other eating-disorder symptoms, while 89.3% met the criteria for at least one DGBI [65].

It is important to note that a positive screening result does not necessarily establish an ARFID diagnosis. ARFID is characterized by persistent restriction associated with clinically significant weight loss or faltering growth, nutritional deficiency, dependence on supplements/EN feeding, or marked psychosocial interference, without restriction being

driven by weight or shape concerns [66]. In medically complex patients, clinicians must also judge whether the degree of restriction exceeds what would be expected from the underlying medical condition alone.

Asides from ARFID, research [49] has also revealed typical eating disorders in EDS, including anorexia (AN) [67–70] and bulimia nervosa (BN). Case reports have also described AN in individuals with EDS/hEDS [68,69]. Furthermore, two Spanish-based studies revealed that among women with EDS, 15.7% suffered from AN, 12.4% exhibited BN [49], while the risk for eating disorders was associated with GI symptom severity [25]. It has been suggested that specific EDS complications including dysphagia, fragility of the oral mucosa, and smell and taste abnormalities may propel food selectivity and disordered eating patterns [67,71]. With this regard, screening for disordered eating, painful eating and fearful eating in EDS using validated tools is essential for prompt identification and comprehensive management.

5.2. POTS

It is known that hEDS/HSD and POTS are frequently reported together, but prevalence estimates vary considerably across studies, and this association does not establish a shared causal mechanism [13,72]. When POTS is objectively diagnosed, increasing oral fluid and sodium intake is a standard non-pharmacological measure intended to expand plasma volume. The AGA clinical practice update suggests approximately 2 L of fluid and 10 g of salt daily as a potential regimen [55], while guidance by the cardiovascular society commonly suggests 2–3 L of water and approximately 10–12 g of Sodium chloride daily, individualized to each patient [73].

In a controlled crossover study of adults with POTS, six days of high Sodium intake increased plasma volume and reduced upright heart rate, orthostatic tachycardia, and standing norepinephrine compared with a very-low-Sodium diet, although abnormalities were not fully normalized [74]. This was a short, small physiological trial, rather than a long-term, EDS-focused outcome study.

Fluid and salt targets should therefore be individualized according to age, body size, climate, activity level, fluid losses, background diet, blood pressure, renal and cardiac status, and concurrent treatments such as fludrocortisone. Oral fluids and food-based sodium sources are generally preferred. Routine chronic IV hydration carries meaningful risks of infection, thrombosis, and device dependence and should remain an exceptional rather than routine intervention [73]. Meals of large volume, particularly carbohydrate-dense food choices, may worsen postprandial orthostatic symptoms in some patients. Small, more frequent meals can be tested, but restrictive low-carbohydrate diets do not consist of an established EDS-specific therapy.

5.3. MCAS

MCAS is frequently self-reported in hEDS/HSD cohorts, yet rigorous evidence for a specific hEDS–POTS–MCAS triad, as opposed to frequent co-occurrence, remains limited [13,72]. Symptoms attributed to mast-cell activation (flushing, pruritus, urticaria, wheeze, tachycardia, abdominal cramping, vomiting, or diarrhea) overlap substantially with DGBI, POTS, medication effects, and ordinary food intolerance [55]. Consequently, the AGA recommends targeted, rather than universal evaluation. Suspected episodes should be assessed with appropriate mediator testing and dedicated allergy/immunology input, rather than assigning the diagnosis empirically [55].

The dietary implications of this uncertainty are nonetheless substantial in practice. In the CANDI-hEDS cohort, 21.3% of participants had already experimented with a low-histamine diet and 79.6% had followed some form of elimination diet [17]. Self-reported

improvement cannot establish a causal or diet-specific effect. Compounding this, no standardized definition of a "low-histamine diet" exists, food histamine content varies substantially with storage and processing, and direct controlled evidence in hEDS or in rigorously diagnosed MCAS remains absent [55,75].

Confirmed IgE-mediated food allergy requires appropriate allergen avoidance; the present concern relates to the empiric elimination for nonspecific symptoms. Established immune-mediated GI disorders, including eosinophilic esophagitis (EoE) and food protein-induced enterocolitis syndrome (FPIES), also require disease-specific dietary management. For suspected non-IgE food triggers or MCAS-related symptoms, however, a short, structured elimination trial with predefined outcome measures and a planned reintroduction phase is considerably safer than an open-ended, expanding list of forbidden foods [76]. Dietitian supervision is particularly important when several major food groups are avoided simultaneously, when the patient is already underweight, when a child is still growing, or when ARFID risk is present. Extensive, prolonged restriction should not be justified based on nonspecific, non-validated commercial food-intolerance panels.

Recent multidisciplinary syntheses have attempted to map these overlapping gastrointestinal, autonomic, and immune contributions to nutritional risk explicitly across the hEDS–POTS–MCAS triad, arguing for integrated rather than fragmented clinical management [77].

6. Micronutrient Deficiencies

6.1. Dietary Inadequacy Versus Confirmed Biochemical Deficiency

The literature supports risk of inadequate intake than a characteristic biochemically proven "EDS nutrient deficiency profile". In the largest dietary analysis to date, the most prominent dietary inadequacies included low fiber intake and insufficient estimated intakes of vitamin D, Potassium, Iron, Magnesium, Copper, Selenium, niacin, riboflavin, and folate, whereas intakes of protein, thiamine, and vitamins A, B12, C, and E were mostly adequate for the majority of participants [14]. These values reflect estimated food intake rather than confirmed serum or tissue deficiency and were derived mainly from adult women in the UK [14].

Among micronutrients, vitamin D has received comparatively greater research attention, although the available evidence remains limited. Preliminary findings from a UK Biobank analysis, indicated lower serum 25-hydroxyvitamin D (25(OH)D) concentrations in women with EDS compared to matched healthy controls, alongside increased odds of deficiency [78]. Another study involving a smaller cohort of women with hypermobile or classical EDS reported 25(OH)D deficiency in 60% of the participants, with secondary hyperparathyroidism being apparent in a subset group [79]. However, the limited methodological information available in these abstracts precludes a comprehensive assessment of study quality and limits the strength of the conclusions that can be drawn. In contrast, a study involving individuals with generalized joint hypermobility rather than confirmed EDS reported similarly high rates of vitamin D deficiency in the hypermobile arm (89.5%) and among controls (84.2%), without observing between-group differences [80].

For Iron, B12, Zinc, Copper, and Selenium, well-designed peer-reviewed biochemical studies specifically in hEDS/HSD are, at the time of writing, essentially absent.

6.2. Deficiency Risk by Clinical Context

Rather than a uniform panel, potential deficiencies are better considered according to the adopted dietary pattern and the underlying clinical context [81]. Iron deficiency, for example, may result from inadequate intake or menstrual and GI blood loss. Bleeding and heavy menstrual bleeding are well documented in EDS more broadly, with menorrhagia

reported in the majority of affected women in some cohorts and life-threatening or surgery-requiring menorrhagia in approximately 14% [82,83]. Vitamin B12, folate, Calcium, Iodine, and Iron warrant attention in vegan or highly restricted diets. Vitamin D and Calcium are relevant when sun exposure, intake, weight-bearing activity, or bone health are suboptimal, while electrolyte abnormalities may arise with vomiting, diarrhea, laxative use, high fluid intake, or artificial nutrition. Selenium, Copper, Zinc, and Magnesium should be assessed selectively, because symptoms attributed to them are nonspecific, and excessive replacement can itself prove harmful.

6.3. Vitamin C, Copper, and Zinc: Mechanistic Plausibility and Its Limits

Vitamin C warrants separate consideration because of its direct biochemical link to collagen biosynthesis. Ascorbate is the essential cofactor for prolyl and lysyl hydroxylases, the enzymes responsible for post-translational hydroxylation of procollagen required for triple-helix stability and secretion. Severe deficiency (scurvy) produces connective-tissue fragility, impaired wound healing, and vascular fragility that can superficially resemble EDS features [84]. This shared final pathway makes vitamin C status a natural focus of interest. Scurvy is a distinct, fully reversible nutritional disease, and hEDS is not caused by vitamin C deficiency; thus, the link involves a mechanistic plausibility, not a shared etiology. A recent study revealed a high prevalence of low vitamin C status in a cohort with hypermobility-related bleeding disorders of unknown cause, raising the question of whether suboptimal vitamin C status could compound bleeding tendency independent of frank scurvy [85]. Consistent with this, the recent dietary study by Topan et al. found adequate estimated vitamin C intake in 92.4% of participants [14]. Testing, or replacement may be appropriate when intake is poor, bruising or bleeding is disproportionate, or other risk factors exist. High-dose vitamin C supplementation as a disease-modifying treatment is unsupported.

Similarly, Copper is the essential co-factor for lysyl oxidase, which cross-links collagen and elastin fibrils [86], and Zinc participates in matrix metalloproteinase (MMP) activity and wound-healing pathways relevant to connective-tissue turnover [87]. Both provide biologically coherent rationales for interest in EDS, but as with vitamin C, no EDS-specific interventional evidence shows that correcting subclinical Copper or Zinc status changes joint, skin, or GI outcomes. Dietary adequacy in the Topan cohort was 58.8% for Copper and 70.8% for Zinc, likely reflecting the same restrictive dietary patterns already described earlier rather than an EDS-specific metabolic defect [14]. Supplementation beyond correction of a documented deficiency carries real risks, as high-dose Zinc may induce Copper deficiency. Similarly, excessive vitamin B6 may cause neuropathy, while high-dose Magnesium commonly causes diarrhea [88,89]. Although Magnesium is frequently promoted for muscle cramps, fatigue, and joint pain in hEDS/HSD, no dedicated controlled trials have established its efficacy for these indications in this population.

7. Body Composition

7.1. Bone Composition and Health

Suboptimal bone health is a common finding among people with hEDS/HSD. Distinct mutations in the type 1 collagen gene can result in different phenotypes, including a classic EDS type, arthrochalasia EDS, mild-to-severe *osteogenesis imperfecta*, or an overlapping phenotype between EDS and *osteogenesis imperfecta* [90].

Research has suggested that within the hEDS/HSD spectrum, BMD does not appear to predict the fracture risk entirely, while low bone quality parameters—including trabecular number, thickness, and connectivity—seem to plays a role in bone strength [90]. In EDS, patients have been shown to attain low BMD [90–92] and low bone quality, leading to

idiopathic osteoporosis [93] and a high risk of morphometric vertebral fractures [94]. Among more prevalent hypermobile and classic EDS types, research has revealed mildly decreased BMD levels, but it has not delineated if fracture rates are also increased [94]. More recently, studies also showed low cortical bone mineral content (BMC) and area in hEDS and generalized HSD [95]. In parallel, hEDS appears to be associated with low trabecular BMC, while generalized HSD is related to lower stress–strain index and periosteal and endosteal circumference [95]. Żuk-Łapan and associates [96] argued that Calcium and phosphate metabolic disturbances are the root cause of bone fractures among patients with hEDS, manifesting as low circulating Phosphorus levels. For this, it is recommended that patients are regularly monitored for Calcium and phosphate metabolism abnormalities [91].

7.2. Muscle Mass and Strength

Few studies have assessed body composition indices in hEDS/HSD, including muscle and fat mass. Coussens [97] evaluated muscle mass in female patients with hEDS, HSD, and healthy controls using dual-energy x-ray absorptiometry (DXA), but failed to record differences between hEDS and HSD groups. Nonetheless, when both patient groups were compared to healthy controls, physical functioning, maximal muscle strength and muscle strength endurance were reduced among the first, suggesting that strength training is a prerequisite in the effective management of hEDS and HSD. Similar findings were also reported in another study, comparing women with hEDS to healthy individuals [98]. In hEDS, lower extremity muscle weakness was substantial, reflected by reduced knee extensor and flexor muscle strength, as well as by several endurance parameters [98]. Decreased muscle strength may further compromise stability of the joints, affecting movement patterns, while inducing injuries in EDS [98]. This observed muscle weakness does not appear to be progressing over time [98], but seems to be the epiphenomenon of muscle dysfunction, rather than reduced muscle mass [98], thereby requiring interventions to improve muscle functioning.

7.3. Fat Mass

One study [99] assessed fat mass in patients with vEDS compared to controls using DXA. The results revealed increased truncal and lower extremities fat, although the total fat mass between groups did not differ. Among women with hEDS/HSD [48], no differences were recorded in fat mass and visceral fat compared to healthy controls.

More evidence is required in order to understand the possible effects of EDS on fat mass.

7.4. Lipedema and EDS

Researchers have also reported cases of lipedema in hEDS/HSD. Lipedema is a loose CTD causing progressive and disproportionate subcutaneous fat accumulation on the extremities [100,101]. As a result, patients with lipedema may often develop eating disorders, in a relentless pursuit of weight loss. Additionally, recent research has revealed common pathophysiological mechanisms between HSD and lipedema. In more detail, among patients with lipedema, 44% reported joint hypermobility and 60% recalled being a hypermobile child, while when compared to health controls, they exhibited more connective-tissue-related motor deficits and systemic symptoms [102]. As the association between EDS and lipedema is apparent, consensus guidelines [103] for the management of lipedema include hypermobile joints in the common comorbid conditions that should be considered. Caution should be given as awareness of lipedema is low among health care professionals and the general public, and this is why it is often mistaken for lifestyle-induced obesity [104], rather than a distinct entity requiring symptom-specific management [105].

7.5. Considerations for Body Composition Assessment in EDS

In EDS, dysautonomia, POTS, gastroparesis and GI symptoms can often induce dehydration and electrolyte imbalances. For this, assessing body composition using bioelectrical impedance analysis (BIA) should be avoided, as fluid imbalances have been shown to affect BIA results [106]. As a result, DXA appears to be the most accurate method to assess body composition among patients with EDS.

8. Dietary Interventions and Supplementation

8.1. Evidence for Dietary Interventions

No specific dietary pattern has been established for EDS. The foundational recommendation across all sources regarding the nutritional management in EDS is a nutritionally complete dietary pattern adapted to the individual's dominant symptom cluster, rather than a fixed prescriptive regimen (Figure 2). Several extrapolated interventions are supported by the adjacent literature: small-particle, low-fat meals for patients with confirmed gastroparesis [63,64], dietitian-supervised low-Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP) trials for patients meeting IBS-type Rome IV criteria, and gluten, or lactose restriction reserved for cases with documented intolerance rather than empiric elimination.

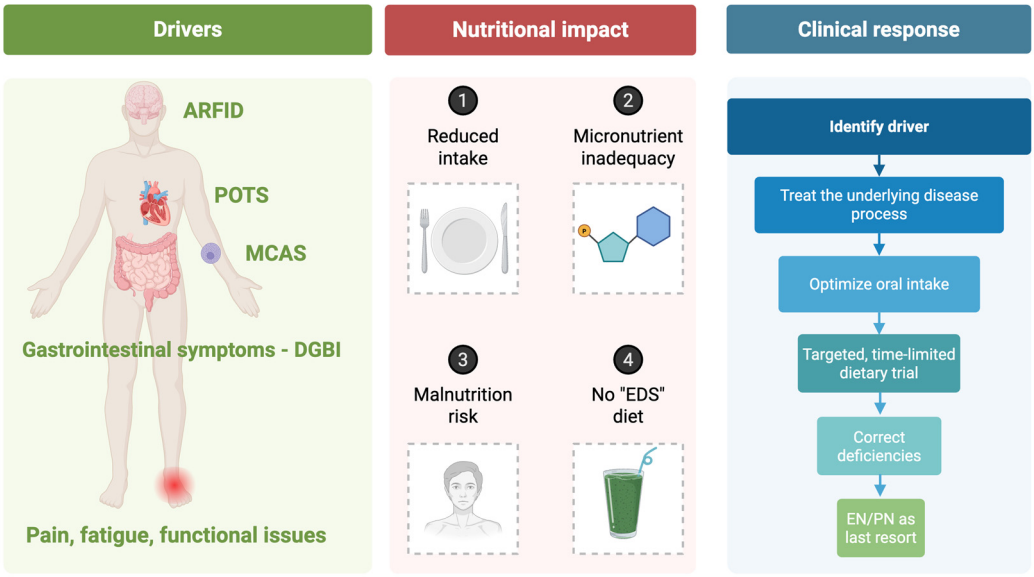


Figure 2. EDS proposed framework. ARFID: avoidant restrictive food intake disorder; DGBI: Disorders of gut–brain interaction; EDS: Ehlers–Danlos syndrome; EN: enteral nutrition; MCAS: mast-cell activation syndrome; PN: parenteral nutrition; POTS: postural tachycardia syndrome.

Additional evidence from related clinical populations provides preliminary, but indirect, insights into the potential role of dietary modification in hEDS/HSD. In a retrospective study of women with POTS without celiac disease, 40% of whom had hEDS and 55% were diagnosed with MCAS, a gluten-free diet (GFD) was associated with a 33.9% reduction in total COMPASS-31 autonomic symptom burden, inducing the greatest improvements in orthostatic intolerance and GI subdomains [107]. The authors explicitly acknowledged that, given the overrepresentation of MCAS and hEDS relative to the general POTS population, the observed benefit could not be attributed to POTS improvement alone; a planned subgroup analysis by comorbidity was not performed, and the retrospective design, absence of a control group, and reliance on recalled baseline scores further limit causal inference [107].

Similarly, among patients with IBS, a low-FODMAP diet produced greater symptom relief in those with joint hypermobility syndrome (JHS) than those without [108]. These observational findings differ from the self-reported results of the CANDI-hEDS cohort [17]. However, differences in patient recruitment, diagnostic classification, outcome assessment and study design preclude direct comparison and do not establish that supervised implementation was responsible for the observed response.

A small prospective, single-arm feasibility study evaluated a nine-week integrative medicine program incorporating recommendations for an anti-inflammatory Mediterranean diet, dietary counseling, self-management, and behavioral and psychosocial support in adults with joint hypermobility and suspected, or diagnosed EDS/HSD [109]. Of the 13 enrolled participants in total, eight completed the study, and adherence to dietary recommendations was limited. Although no change was recorded in pain sensation, improvements in fatigue and selected measures of satisfaction with care were reported. Importantly, the absence of a control arm, the underpowered sample, incomplete diagnostic confirmation, and multicomponent intervention preclude conclusions regarding the independent efficacy of the dietary component.

Thus, although preliminary uncontrolled intervention data are available, adequately powered controlled trials evaluating the efficacy of specific dietary interventions in diagnostically well-characterized EDS/HSD populations are still lacking.

8.2. Micronutrient Supplementation

Topan et al. reported that 61% of the participants in the CANDI-hEDS cohort used at least one dietary supplement, most frequently involving vitamins D, C, B-complex, and Magnesium, mainly self-initiated by the patients instead of being suggested by a clinician [17]. The reasons behind supplement use were not established in this analysis. Such use may reflect concerns about dietary adequacy or attempts to manage symptoms, but should not be interpreted as evidence of biochemically confirmed deficiencies or therapeutic benefit.

Mantle et al. [110] proposed a multicomponent supplementation regimen, including vitamin C, Magnesium, methylsulfonylmethane, silica, pycnogenol, carnitine, and coenzyme Q10, hypothesizing potential benefits for collagen synthesis and connective-tissue integrity. However, this remains an untested hypothesis, with no controlled clinical evidence demonstrating improvements in EDS-related outcomes.

Given the limited EDS/HSD-specific interventional evidence, nutritional management relies largely on general clinical nutrition principles and effective interventions extrapolated from related conditions. Table 4 presents a pragmatic hierarchy of nutritional interventions rather than a validated disease-specific algorithm. Its steps may be adapted, or implemented in parallel, according to individual clinical needs, with particular caution regarding invasive nutritional support.

Table 4. A tiered hierarchy for nutritional intervention in EDS/HSD.

Step	Action	Rationale
1	Define the problem	Characterize the dominant symptom driver (dysmotility, ARFID, MCAS-related restriction, malabsorption) before intervening—avoid empiric elimination as a first step. Identify nutritional deficiencies [14,17,22].
2	Treat the underlying disease process	Manage POTS, MCAS, gastroparesis, or pelvic-floor dysfunction directly where identifiable [22,73].
3	Optimize oral intake	Food-first strategies: meal texture/frequency modification, adequate hydration and Sodium for POTS, opting for nutritionally complete diet patterns [22,73].

Table 4. *Cont.*

Step	Action	Rationale
4	Targeted, time-limited dietary trial	Dietitian-supervised low-FODMAP, gluten-free, or low-histamine trial, only when clinically indicated, with defined endpoints and ARFID monitoring [55,107,108].
5	Correct confirmed micronutrient deficiencies	Correct documented or strongly suspected deficiencies based on dietary, clinical and, where appropriate, biochemical assessment [14,17].
6	Opt for EN	Reserved for failure of oral strategies after multidisciplinary assessment. When clinically safe, use a time-limited enteral trial before permanent access and preserve oral feeding experiences, particularly in children. Intensive feeding rehabilitation may avert permanent surgical access in selected patients, although current evidence is limited to case reports [111].
7	Opt for PN	Last resort, given documented risks associated with central venous access and PN [22,112].

ARFID: avoidant/restrictive food intake disorder; EN: enteral nutrition; FODMAP: Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols; MCAS: Mast-Cell Activation Syndrome; PN: parenteral nutrition; POTS: Postural Orthostatic Tachycardia Syndrome.

9. Nutritional Management

9.1. Nutritional Recommendations

Although GI manifestations and the broader symptomatology of EDS/HSD are well described, few studies provide specific nutritional guidelines. Nevertheless, several useful recommendations are available from the Ehlers–Danlos Society [113]. Table 5 presents an overview of relevant symptoms and corresponding nutrition-based guidance. A balanced and varied diet, emphasizing whole foods, vegetables, fruit, nuts, seeds, and sources of healthy fats, may support overall dietary adequacy [113]. However, dietary recommendations should be individualized according to nutritional requirements, Gl symptoms, and food tolerability.

Table 5. Nutritional recommendations based on EDS symptomatology.

Symptom	Recommendations
ARFID/disordered eating risk	Screen in food avoidance, fear of symptoms from eating, low intake, weight loss, nutritional deficiencies, supplement/EN dependence, or significant psychosocial impairment occurs. In cases of severe malnutrition, short-term enteral tube feeding may be required as a bridge to multidisciplinary treatment, with the feeding route determined by individual clinical indications [22].
Celiac disease	Follow a gluten-free diet. Consider supplementation with vitamins A, D, E, B12, Copper, Zinc, folate, and Iron due to malabsorption [114].
Constipation	Increase intake of soluble fiber (e.g., kiwi, oats, flax) with increased fluid intake [114].
Diarrhea, bloating and flatulence	Low-FODMAP diet, gluten-free diet when appropriate, soluble fiber, probiotics, and treatment of SIBO when present [115].
Dysphagia	Modify food texture by blending, mashing, or mincing foods [114]. Consider applying the IDDSI [116].
Early satiety/ postprandial fullness	Eat small, frequent meals; eat slowly; chew well [114].
Electrolyte Issues	EN may be considered, using nasogastric or post-pyloric feeding according to the site of GI dysfunction [22]. Use isotonic fluids to support rehydration and preserve intravascular volume.

Table 5. *Cont.*

Symptom	Recommendations
Food triggers/IBS	Use elimination diets for a short period of time; minimize histamine load [76]. Maybe try gluten- and lactose-free diets, if intolerance is apparent. If symptoms do not improve, consider a low FODMAP diet [114].
Gastroparesis	Eat small, frequent meals. Modify food texture by blending, mashing, or mincing foods [114]. If malnutrition exists, a trial of NJ feeding may be considered, with transition to longer-term post-pyloric EN feeding, if tolerated and clinically indicated [22].
GERD	Eat small, frequent meals; eat slowly [114].
Micronutrient deficiencies	Assess dietary intake and investigate suspected micronutrient deficiencies based on clinical findings, dietary restrictions, and targeted laboratory testing. Provide individualized supplementation when clinically indicated, particularly to correct documented deficiencies. Routine high-dose supplementation with vitamins C or E, Zinc, or Selenium is not supported by EDS/HSD-specific evidence [81].
POTS	Increase oral fluid and Sodium intake. Consider smaller, more frequent meals, if large meals worsen symptoms. Gradual rising from supine and sitting positions, especially in the morning, after meals, and after urination/defecation [74,117]. In cases of significant body weight loss or inadequate oral intake, consider nutritional assessment and EN, when indicated. Reserve PN for established indications, such as intestinal failure [22,118].

ARFID: avoidant/restrictive food intake disorder; EN: enteral nutrition; FODMAP: Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols; GERD: gastroesophageal reflux disease; GI: gastrointestinal; IBS: irritable bowel syndrome; IDDSI: International Dysphagia Diet Standardisation Initiative [116]; NJ: nasojejunal; PN: parenteral nutrition; POTS: Postural Orthostatic Tachycardia Syndrome; SIBO: small intestinal bacterial overgrowth.

9.2. Protein Intake

Adequate dietary protein intake is important for maintaining muscle mass, supporting tissue repair, and preserving musculoskeletal function [119]. However, evidence that specific protein sources or supplementation strategies improve musculoskeletal outcomes in hEDS/HSD remains lacking [14,17]. Protein intake should therefore be individualized according to nutritional requirements, dietary preferences, and food tolerability, particularly among patients with GI symptoms or restrictive eating patterns.

9.3. Enteral and Parenteral Nutrition

Escalation to EN or PN may be indicated in selected patients, but it should be based on demonstrated nutritional need and GI dysfunction, rather than symptom severity alone. The use of nutritional support in hEDS/HSD has been reported despite limited evidence of objectively confirmed enteric dysmotility in some cohorts [60]. This discrepancy raises the possibility that additional factors, including restrictive eating, visceral hypersensitivity, and fear-avoidance, may contribute to nutritional difficulties and decisions regarding escalation of support. However, their relative contributions remain uncertain.

Management should therefore follow the least-invasive effective route. First, oral intake should be optimized with symptom treatment, texture or meal modification, oral supplements, and behavioral or psychological care when fear or avoidance is present. The International Dysphagia Diet Standardisation Initiative (IDDSI) framework could be implemented to standardize food textures and liquid consistencies [116]. If oral intake remains insufficient and the GI tract is functional, a time-limited nasogastric or nasojejunal trial can test tolerance before committing to long-term access. The feeding route should match objectively defined physiology. Post-pyloric feeding is not automatically indicated by nausea alone. Goals should include nutritional stabilization, functional recovery, presentation of safe oral experiences and, where feasible, return toward oral intake, consistent

with expert guidance recommending EN when oral strategies fail, within a coordinated, multidisciplinary, biopsychosocial care model [77].

A pediatric case report illustrates the potential value of intensive multidisciplinary intervention before permanent enteral access is established. Kilgore described a 14-year-old patient with hEDS, POTS, mast-cell dysregulation, chronic pain, and severe feeding-related symptoms, who had lost more than 10% of usual body weight, consumed only 25–50% of estimated nutritional requirements, and demonstrated a decline in BMI z-score from −1.0 to −1.9 [111]. During a 10-day inpatient protocol, the nasojejunal tube was removed and oral intake was advanced through coordinated feeding therapy, dietetic care, pelvic-floor physiotherapy and biofeedback, psychological support, treatment of rumination, and optimization of symptom-directed medication. Fourteen months later, the patient maintained all nutrition and hydration orally and had gained 19 lb. Although a single case cannot establish treatment efficacy or determine which component of the intervention was responsible, it demonstrates that severe feeding intolerance in hEDS may be reversible and supports a structured multidisciplinary trial, before permanent surgical feeding access is pursued, when deemed clinically safe [111].

PN should be reserved for intestinal failure or selected situations where adequate nutrition cannot be maintained through other routes. A joint position paper from the European Society for Clinical Nutrition and Metabolism, the European Society of Neurogastroenterology and Motility, and the Rome Foundation cautions against long-term parenteral support in patients without confirmed intestinal failure [120]. Possible risks include catheter infection, thrombosis, loss of venous access, metabolic and hepatobiliary complications, and reduced quality of life. In vEDS, tissue and vascular fragility may add procedural concern, although comparative device-risk data are lacking.

A recent case report described a young woman with hEDS, POTS, and MCAS who experienced repeated premature failure of central venous access during PN due to an abnormal subcutaneous fibrinoid reaction around the catheter site [121]. Switching to post-pyloric EN resolved the access-related complications, restored intestinal function, and improved quality of life [121].

IV fluids may have a short-term role in exceptional decompensation, but chronic central access solely for orthostatic symptoms is difficult to justify, particularly when oral strategies remain possible for POTS [73]. Decisions regarding initiation and continuation of nutrition support are best made by an integrated team including gastroenterology, dietetics, psychology/psychiatry, the primary EDS clinician, and an intestinal-failure service when PN is considered [22,77,120].

10. Pediatric Considerations

10.1. Terminology and Diagnostic Framework

Children and adolescents with EDS represent a distinct patient population whose management requires particular care and should be tailored to their age, developmental stage, growth trajectory, body size and pubertal status. The 2017 hEDS diagnostic criteria were developed for biologically mature individuals and do not transfer directly to pediatric patients [1]. A 2023 pediatric diagnostic framework instead, recommends classifying children according to generalized joint hypermobility, skin/tissue features, musculoskeletal complications, and core comorbidities, reserving the hEDS label for biologically mature adolescents, who meet the adult criteria [122]. Studies using older labels such as “JHS” or “hEDS” for young children should therefore be interpreted in their historical context, rather than assumed equivalent to the adult diagnostic category.

10.2. Gastrointestinal Manifestations in Pediatric Cohorts

Direct pediatric GI data are limited but broadly consistent with their adult counterparts, while also revealing findings with distinct clinical implications. In a tertiary retrospective cohort of 435 patients aged 5–28 years with hEDS/JHS and GI symptoms, constipation was recorded in 61%, dysphagia in 32%, dyspepsia and/or gastroparesis in 25%, EoE in 21%, and celiac disease in 4%; of the 80 patients who underwent motility testing, 31% demonstrated an abnormal test result [50]. However, the inclusion of young adults and the incomplete application of diagnostic testing preclude population-prevalence estimates. Nevertheless, when dysphagia, persistent vomiting, pain, or growth compromise is present in a hypermobile child, targeted evaluation for eosinophilic, celiac, structural, or motility disease may be warranted.

Earlier tertiary referral data similarly suggested a link between complex functional GI presentations and joint hypermobility. Among patients referred to a pediatric neurogastroenterology and autonomic disorders clinic [123], those with a recorded Beighton score had greater chances of exhibiting joint hypermobility compared to their healthy counterparts (OR: 10.03; 95% CI: 5.26–19.13). The risk of POTS was also apparent, but it was unrelated to joint hypermobility. On the other hand, chronic nausea, fatigue, dizziness, migraine, and sleep disturbance were also frequently reported. These findings demonstrate substantial multisystem comorbidity among young patients with complex functional gastrointestinal disorders (FGIDs), but their generalizability is limited by the small referral-enriched sample, retrospective design, inclusion of young adults, and assessment of joint hypermobility rather than hEDS according to current criteria [123].

Community-based studies have not consistently reproduced the high prevalence observed in specialist clinics. In a school-based study, Saps failed to observe any association between functional GI disorders and joint hypermobility in the matched analysis (OR: 1.03; 95% CI: 0.59–1.81) [124]. Similarly, Shulman reported that the prevalence of joint hypermobility did not differ among children with IBS, functional abdominal pain, or no abdominal pain, and neither the presence, nor the severity of hypermobility correlated with abdominal pain or stool characteristics [125]. Collectively, these findings suggest that the pronounced overlap reported in tertiary-care cohorts may partly reflect referral enrichment, greater clinical complexity, or the selection of patients with multisystem symptoms, rather than an association that applies uniformly across pediatric populations [124,125].

In contrast to these smaller community studies, Zloof identified a significant association between HSD/hEDS and IBS in a nationwide study of Israeli adolescents [8]. Among those with hEDS/HSD, 1.5% had specialist-confirmed IBS compared with 0.5% of adolescents without hEDS/HSD. The association remained significant after adjustment for demographic and anthropometric factors (OR: 2.58; 95% CI: 2.02–3.24) and was observed in both sexes [8]. The low absolute prevalence probably reflects the study's stringent case definition and the likelihood that milder IBS was not captured. Nevertheless, its population-based design and specialist-confirmed diagnoses provide stronger epidemiological evidence than referral-centre studies, although the findings concern late adolescence and cannot be generalized directly to younger children [8].

The relationship with autonomic dysfunction is also complex. In a school-based study, Velasco-Benitez compared children with FGIDs to healthy controls and observed that those with FGIDs reported more symptoms of orthostatic intolerance, particularly during orthostasis [126]. However, they were not found to be more likely to meet objective criteria for POTS or orthostatic hypotension, and joint hypermobility was not associated with a greater prevalence of these autonomic diagnoses. These findings suggest that orthostatic symptoms may contribute to the clinical burden of pediatric FGIDs without necessarily demonstrating

a direct causal pathway between joint hypermobility and objectively confirmed autonomic dysfunction [126].

The prevalence of HSD and orthostatic intolerance in DGBI has been suggested to be 46% and 43%, respectively [127]. Patients with both HSD and orthostatic intolerance report worse nausea, disability, depression, and somatic symptom burden compared to those with either alone, or neither [127]. This finding supports the need for integrated, multisystem assessment in symptomatic referral populations, but does not by itself establish causality. For this, it should be interpreted alongside community studies that have not consistently demonstrated an association between joint hypermobility and objectively confirmed autonomic dysfunction [126,127]. Table 6 summarizes the pediatric and adolescent evidence on GI manifestations, hypermobility, and autonomic dysfunction.

Table 6. Evidence on GI manifestations, joint hypermobility, and autonomic dysfunction in children and adolescents.

First Author	Population	Main Findings
Sood [50]	N = 435 patients aged 5–28 years old with hEDS/JHS and GI symptoms; tertiary care	Constipation: 61%; dysphagia: 32%; dyspepsia and/or gastroparesis: 25%; EoE: 21%; CD: 4%. Motility testing was abnormal in 25/80 patients tested (31%).
Kovacic [123]	N = 66 patients aged 5–24 years old; pediatric neuro-gastroenterology and autonomic disorders clinic	Joint hypermobility occurred in 56% of the 45 patients assessed using Beighton scoring. Compared to published healthy adolescent populations, OR was 10.03 (95% CI: 5.26–19.13). POTS occurred in 34% overall and did not correlate with hypermobility.
Saps [124]	N = 654 children; school-based study; matched analysis included n = 136 children with FGIDs and n = 136 healthy controls	No association between FGIDs and joint hypermobility in the matched analysis (OR: 1.03; 95% CI: 0.59–1.81). Hypermobility was defined as Beighton score ≥4.
Shulman [125]	N = 219 children aged 7–12 years old with IBS, functional abdominal pain, or no abdominal pain	Hypermobility prevalence and Beighton scores were similar across groups. Hypermobility did not correlate with abdominal pain or stooling characteristics. Some associations with child-reported somatization and depression were observed.
Zloof [8]	N = 1,627,345 Israeli adolescents aged 16–19 years old, including n = 4686 with hEDS/HSD; nationwide population-based study	Specialist-confirmed IBS occurred in 1.5% of adolescents with hEDS/HSD versus 0.5% without. The association persisted after adjustment (OR: 2.58; 95% CI: 2.02–3.24) and was observed in both sexes.
Velasco-Benitez [126]	N = 155 children with FGIDs and N = 151 controls; school-based study	Children with FGIDs reported more orthostatic symptoms but were not more likely to meet objective criteria for POTS or orthostatic hypotension. Joint hypermobility was not associated with either diagnosis.
Santucci [127]	N = 175 patients aged 9–21 years old; multidisciplinary referral clinic	HSD was identified in 46% and orthostatic intolerance in 43%. Participants with both had worse nausea, disability, depression, and somatic symptom burden than those with either alone, or neither.

CD: Celiac Disease; CI: confidence intervals; DGBI: disorders of gut–brain interaction; EoE: eosinophilic esophagitis; FGIDs: functional gastrointestinal disorders; GI: gastrointestinal; hEDS: hypermobile Ehlers–Danlos syndrome; HSD: hypermobility spectrum disorder; IBS: irritable bowel syndrome; JHS: joint hypermobility syndrome; OR: odds ratio; POTS: postural orthostatic tachycardia syndrome.

10.3. Growth and Nutritional Assessment

As normal childhood involves active linear growth and pubertal development, pediatric nutritional assessment must prioritize longitudinal weight, height/length, BMI-for-age,

pubertal development, and growth velocity, rather than adult BMI thresholds or single-point measurements. Clinicians should also evaluate feeding skills, chewing and swallowing, oral-motor fatigue, dental and temporomandibular problems, sensory sensitivities, school-day intake, family mealtime dynamics, constipation, and the functional impact of pain or orthostatic symptoms on eating. Pediatric feeding disorder, ARFID, and appetite loss secondary to GI disease overlap considerably, but are not interchangeable. Therefore, assessment is recommended to encompass medical, nutritional, feeding-skills, and psychosocial domains rather than defaulting to any single explanatory framework.

10.4. Dietary and Nutrition-Support Considerations Specific to Children

Elimination diets carry particular risks when implemented during periods of active growth and are recommended only when a clear diagnostic or therapeutic purpose is set, with age-appropriate nutritional substitutions, and early, planned reintroduction, if ineffective. Salt and fluid recommendations for pediatric POTS must be individualized by the pediatric management team, rather than copied directly from adult targets. When tube feeding is required, it should support growth and participation in normal childhood activities, while preserving safe oral experiences and maintaining a defined reassessment plan. The pediatric case described above illustrates that intensive multidisciplinary rehabilitation may restore oral intake and avert permanent surgical feeding access in selected patients with hEDS and severe functional feeding intolerance [111]. However, this remains case-level evidence and should not be interpreted as justification for withholding EN when objective nutritional compromise cannot be corrected safely by oral strategies. Decisions regarding permanent access should incorporate nutritional severity, GI physiology, feeding skills, autonomic symptoms, psychological factors, and each child's developmental and social needs.

10.5. Clinical Implications

Effective pediatric hEDS/HSD nutritional care requires family-centered goals and close coordination among pediatrics, gastroenterology, dietetics, psychology, feeding therapy, physiotherapy, and school services. In practice, this means: (i) using age-appropriate diagnostic terminology rather than adult criteria; (ii) excluding structural and eosinophilic GI disease before defaulting to a functional diagnosis; (iii) tracking growth and pubertal trajectory as pediatric-specific markers of nutritional adequacy; (iv) assessing feeding across medical, nutritional, skill-based, and psychosocial domains; (v) evaluating orthostatic symptoms and treating objectively confirmed orthostatic intolerance as part of integrated GI and nutritional management, while avoiding the assumption that joint hypermobility establishes POTS, or a causal autonomic mechanism [126,127]; and (vi) discussing permanent feeding access, only after multidisciplinary assessment has been conducted and, when clinically safe, a structured trial of conservative feeding rehabilitation [111].

11. Research Gaps and Priorities

In clinical practice, the findings support assessing dietary intake, recent weight change, and the extent of food restriction in people with hEDS/HSD, even when BMI is within the normal range. This assessment can help clinicians identify patients who may benefit from dietetic support, address gastrointestinal or autonomic symptoms that interfere with eating, and prioritize adequate oral intake. Given the limited evidence for the effectiveness of specific diets and dietary supplements, dietary restrictions should have a clear indication and be reassessed for benefit and nutritional adequacy. EN or PN should be considered when there is an established clinical indication, following multidisciplinary assessment.

11.1. Population and Study Design Limitations

Nearly all quantitative evidence reviewed here derives from a small number of overlapping UK cohorts (principally CANDI-hEDS and its follow-up analyses), which include predominantly female, Caucasian, adult patients, recruited from tertiary neurogastroenterology clinics or patient-advocacy groups [14,17]. By contrast, the broader epidemiology of GI symptoms now includes large electronic-health-record studies, a nationwide adolescent cohort, and a formal meta-analysis [8,20,54], but these sources provide little detailed information on the dietary intake, biochemical nutritional status, body composition, or the outcomes of nutritional interventions. This concentration of evidence in a narrow demographic and geographic base limits generalizability to men, non-Caucasian populations, and non-UK healthcare and dietary contexts. Cross-sectional designs dominate the available literature. None of the key studies discussed can establish whether dietary restriction, GI symptoms, or autonomic dysfunction are cause, consequence, or mutually reinforcing, and prospective, longitudinal cohorts are required to disentangle this bidirectionality. The substantial heterogeneity observed in the recent meta-analysis further indicates that pooled prevalence estimates cannot resolve the effects of different diagnostic criteria, referral setting, age, sex, and symptom ascertainment, without more standardized prospective studies [20]. Most of the available evidence on nutritional status and management comes from individuals with hEDS or HSD. Nutritional data for other EDS subtypes remains very limited. Consequently, the nutritional findings and management considerations discussed in this review may have limited applicability to other EDS subtypes.

11.2. Interventional and Biochemical Evidence Gaps

Several critical gaps limit the evidence base of this review. Controlled dietary intervention trials in diagnostically well-characterized hEDS/HSD populations are still lacking. Although a small, uncontrolled feasibility study has evaluated a multicomponent integrative medicine program incorporating dietary recommendations [109], its design does not permit conclusions regarding the efficacy of the prescribed diet. Other available intervention data derive primarily from related, but distinct populations [107,108], while connective-tissue-targeted supplementation remains supported only by untested hypotheses [110]. Consequently, recommendations regarding the nutritional management are largely extrapolated from general or comorbidity-specific guidance, highlighting the need for adequately powered, controlled EDS/HSD-specific trials.

Secondly, biochemical and mechanistic data remain sparse. Biochemical evidence remains limited, with vitamin D being the most frequently investigated micronutrient, although much of the available EDS-specific evidence is preliminary, including findings reported only in conference abstracts. Dedicated studies assessing confirmed biochemically deficiencies regarding Iron, vitamin B12, Zinc, Copper, and Selenium in hEDS/HSD, remain scarce. Also, the mechanistic link between connective-tissue abnormality and GI dysfunction remains unresolved for hEDS specifically, since the collagen-defect mechanism established for vascular and classical EDS does not transfer to a subtype with no identified molecular basis.

The next research gap is related to a persistent unresolved clinical paradox: patients with hEDS/HSD receive EN/PN support at high rates, despite not exhibiting greater—and in one study lower—rates of enteric dysmotility, and whether this reflects visceral hypersensitivity, autonomic factors, fear-avoidance, or practice variation, remains untested via a prospective study design. Finally, the lack of malnutrition screening tools, dietary-pattern classification, or diagnostic instruments validated specifically for this population is apparent. Current nutritional assessment, therefore, largely builds on frameworks developed for other

clinical populations. Developing hEDS/HSD-specific tools represents a concrete, achievable research priority.

11.3. Pediatric-Specific Gaps

Pediatric evidence remains substantially less developed than the adult literature. One large nationwide study provides population-based evidence for an association between HSD/hEDS and IBS in late adolescence [8], but most studies involving younger children remain underpowered, cross-sectional or retrospective, and enriched with patients referred to specialist GI, autonomic, or multidisciplinary services [50,123–127]. Moreover, studies of joint hypermobility cannot be assumed as representative of children with hEDS according to current diagnostic frameworks. No study thus far has prospectively examined dietary intake, biochemical micronutrient status, body composition, growth, or pubertal outcomes in relation to a nutritional intervention in children with hEDS/HSD. Evidence concerning intensive feeding rehabilitation and avoidance of permanent surgical feeding access is currently limited to a single case report [111]. The lack of comparative studies evaluating conservative multidisciplinary management against different forms of enteral support is also apparent. Prospective pediatric cohorts using age-appropriate hypermobility classifications, longitudinal growth outcomes, standardized nutritional assessment, and clearly defined feeding endpoints therefore represent a major research priority.

Future research should prioritize multicenter prospective cohorts and controlled dietary intervention studies. Cohorts should use standardized diagnostic criteria, report hEDS and HSD separately, and recruit participants with other EDS subtypes, whenever feasible. Repeated measures of dietary intake, biochemical micronutrient status, and GI symptoms would help clarify how these outcomes change over time. Controlled trials should assess whether targeted dietary interventions improve symptoms, while ensuring nutritional adequacy. Pediatric studies should also track linear growth and feeding outcomes using age-appropriate measures.

12. Conclusions

Nutritional concerns are clinically relevant in hEDS/HSD, although the currently available evidence remains limited and heterogeneous. GI symptoms, restrictive eating, autonomic dysfunction, and functional limitations may compromise dietary adequacy, even in patients with normal or elevated BMI. These findings support individualized nutritional assessment rather than a universal "EDS diet" or routine dietary supplementation.

Management should prioritize identifiable GI and autonomic disorders, optimization of oral intake, and targeted correction of underlying nutritional deficiencies. Dietary restrictions should be appropriately supervised, while the use of EN or PN should be reserved for established indications following multidisciplinary assessment. In children, nutritional management should additionally consider adequate growth, feeding skills, and psychosocial functioning.

Future research should prioritize prospective interventional studies, objective biochemical assessment of nutritional status, and pediatric-specific investigations to establish evidence-based nutritional management strategies.

Author Contributions: Conceptualization, M.G.G. and D.P.B.; methodology, A.G. (Athanasios Gkoutzourelas), A.G. (Arriana Gkouvi), E.C.P. and M.G.G.; software, E.C.P. and A.G. (Arriana Gkouvi); investigation, A.G. (Athanasios Gkoutzourelas), A.G. (Arriana Gkouvi), E.C.P. and M.G.G.; resources, D.P.B. and M.G.G.; data curation, E.C.P., A.G. (Arriana Gkouvi), A.G. (Athanasios Gkoutzourelas), and M.G.G.; writing—original draft preparation, A.G. (Athanasios Gkoutzourelas), A.G. (Arriana Gkouvi), and E.C.P.; writing—review and editing, A.G. (Athanasios Gkoutzourelas), A.G. (Arriana Gkouvi), E.C.P., P.S.P., D.G.G., D.P.B. and M.G.G.; visualization, E.C.P. and A.G. (Arriana Gkouvi);

supervision, M.G.G., D.G.G. and D.P.B.; project administration, M.G.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: Part of the present work was presented at the 33rd European Paediatric Rheumatology Congress, conducted in Belgrade, Serbia, in 2026.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
25(OH)D	25-hydroxyvitamin D
ACG	American College of Gastroenterology
AD	Autosomal dominant
AEBP1	Adipocyte enhancer-binding protein 1
aEDS	Arthrochalasia Ehlers–Danlos syndrome
AGA	American Gastroenterological Association
AN	Anorexia nervosa
AR	Autosomal recessive
ARFID	Avoidant/restrictive food intake disorder
BIA	Bioelectrical impedance analysis
BMC	Bone mineral content
BMD	Body mineral density
BMI	Body mass index
BN	Bulimia nervosa
CANDI-hEDS	Comprehensive Assessment of Nutrition and Dietary Influences in hEDS
CD	Celiac disease
CI	Confidence interval
clEDS2	Classical-like EDS type 2
COMPASS-31	Composite Autonomic Symptom Score-31
CTD	Connective-tissue disease
cvEDS	Cardiac-valvular Ehlers–Danlos syndrome
dEDS	Dermatosparaxis Ehlers–Danlos syndrome
DXA	Dual-energy x-ray absorptiometry
DGBI	Disorders of gut–brain interaction
EAR	Estimated average requirements
EDS	Ehlers–Danlos syndromes
EoE	eosinophilic esophagitis
FGIDs	Functional gastrointestinal disorders
FODMAP	Fermentable oligosaccharides, disaccharides, and polyols
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GFD	Gluten-free diet
GLIM	Global Leadership Initiative on Malnutrition
GMO	Genetically modified organisms
hEDS	Hypermobile EDS
HSD	Hypermobile spectrum disorders
IBS	Irritable bowel syndrome

ICD	International Classification of Diseases
IV	Intravenous
JHS	joint hypermobility syndrome
kEDS	Kyphoscoliotic Ehlers–Danlos syndrome
MCAS	Mast-cell activation syndrome
mcEDS	Musculocontractural Ehlers–Danlos syndrome
mEDS	Myopathic Ehlers–Danlos syndrome
MNA	Mini Nutritional Assessment
MMP	Matrix metalloproteinase
MSM	Methylsulfonylmethane
MUST	Malnutrition Universal Screening Tool
NRS-2002	Nutritional Risk Screening-2002
OR	Odds ratio
pEDS	Periodontal Ehlers–Danlos syndrome
PG-SGA	Patient-Generated Subjective Global Assessment
POTS	Postural orthostatic tachycardia syndrome
RA	Rheumatoid arthritis
SFA	Saturated fatty acids
SIBO	Small intestinal bacterial overgrowth
SIMD	Small intestinal microbial dysbiosis
spEDS	Spondylodysplastic Ehlers–Danlos syndrome
vEDS	Vascular EDS
UK	United Kingdom

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