ARTICLE

Gastrointestinal and Nutritional Issues in Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type

MARCO CASTORI, SILVIA MORLINO, GIULIA PASCOLINI, CARLO BLUNDO, AND PAOLA GRAMMATICO

Gastrointestinal involvement is a well known complication of Ehlers–Danlos syndromes (EDSs), mainly in form of abdominal emergencies due to intestinal/abdominal vessels rupture in vascular EDS. In the last decade, a growing number of works investigated the relationship between a wide spectrum of chronic gastrointestinal complaints and various EDS forms, among which the hypermobility type (a.k.a. joint hypermobility syndrome; JHS/EDS-HT) was the most studied. The emerging findings depict a major role for gastrointestinal involvement in the health status and, consequently, management of JHS/EDS-HT patients. Nevertheless, fragmentation of knowledge limits its impact on practice within the boundaries of highly specialized clinics. In this paper, literature review on gastrointestinal manifestations in JHS/EDS-HT was carried out and identified papers categorized as (i) case-control/cohort studies associating (apparently non-syndromic) joint hypermobility and gastrointestinal involvement, (ii) case-control/cohort studies associating JHS/EDS-HT and gastrointestinal involvement, (iii) case reports/series on various gastrointestinal complications in (presumed) JHS/EDS-HT, and (iv) studies reporting gastrointestinal features in heterogeneous EDS patients' cohorts. Gastrointestinal manifestations of JHS/EDS-HT were organized and discussed in two categories, including structural anomalies (i.e., abdominal/diaphragmatic hernias, internal organ/pelvic prolapses, intestinal intussusceptions) and functional features (i.e., dysphagia, gastro-esophageal reflux, dyspepsia, recurrent abdominal pain, constipation/diarrhea), with emphasis on practice and future implications. In the second part of this paper, a summary of possible nutritional interventions in JHS/EDS-HT was presented. Supplementation strategies were borrowed from data available for general population with minor modifications in the light of recent discoveries in the pathogenesis of selected JHS/EDS-HT features. © 2015 Wiley Periodicals, Inc.

KEY WORDS: abdominal pain; constipation; diet; Ehlers–Danlos syndrome; nutraceuticals

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INTRODUCTION

Gastrointestinal (GI) involvement of EDS is known since the late seventies [Beighton et al., 1969]. For many years, the attention of researchers and clinicians was mostly attracted by the life-threatening complications of vascular EDS, which features spontaneous bowel and abdominal vessel ruptures [Beighton et al., 1998]. However, literature also accounts some papers pointing out a wider spectrum of GI manifestations in various forms of EDS [Burcharth and Rosenberg, 2012]. The awareness on the impact of GI manifestations to the health status of EDS patients rose in the last decade, when Hakim and Grahame [2004] found a high rate of various functional GI complaints in adults with joint hypermobility syndrome (a.k.a. Ehlers–Danlos syndrome, hypermobility type; JHS/EDS-HT). Accordingly, Levy [2012] listed functional bowel disorders as an "unofficial" minor diagnostic item in the 2004 version of his reference paper on JHS/EDS-HT. Since then, a growing number of works presented data on the spectrum, rate and possible pathogenesis of GI manifestations in JHS/EDS-HT [see below]. However, while actual knowledge accounts a number of studies highlighting the impact of GI manifestations in JHS/EDS-HT, the emerging results still depict a fragmented picture which lays on the heterogeneous and, occasionally, divergent perspectives of the involved research groups.

In the first part of this paper, we carried out a review of available data with the aim of offering a comprehensive summary of GI involvement in JHS/EDS-HT. We also tried to present a wider perspective by speculating on pathogenesis and actual management approach. As a side aspect of GI involvement in EDS, Mantle et al. [2005] proposed a set of nutritional interventions purportedly aimed at improving selected disease manifestations of this condition. The possible applications of this resource was reinforced by Tinkle [2010]; who reported his experience on nutraceuticals in his monograph on JHS/EDS-HT. Research on nutritional interventions in EDS is still in its infancy. Nevertheless, data on the possible beneficial effects of an increasing number of nutraceuticals in many chronic complaints commonly encountered in JHS/EDS-HT is now available for the general population. In the second part of this paper, we present a summary of actual knowledge and theoretical applications of nutritional therapy in the management of some disease aspects of JHS/EDS-HT.

METHODS

This study consisted in a PubMed search with the following research string: ["Ehlers–Danlos syndrome" OR EDS OR hypermobility] AND [abdominal OR anal OR bowel OR colonic OR constipation OR diarrhea OR dysphagia OR esophagus OR gastric OR gastrointestinal OR gut OR liver OR prolapse OR rectal]. All relevant articles detected in this phase were further scrutinized for additional references not appeared in this search. Review or hypothesis papers without novel data were excluded from the Results section, while their contents were used for interpretation of collected information. All papers clearly concerning EDS subtypes other than JHS/EDS-HT (mainly, vascular and classic EDS) were equally excluded. Case-control studies relating GI manifestations with non-syndromic/unclassified generalized joint hypermobility (gJHM), and case-control and case series works investigating GI involvement in patients with unclassified EDS or belonging to various EDS subtypes were included, but their results were presented separately. Inclusion of these works was based on the following: (1) at the moment, apparently isolated gJHM blurs within the increasingly wide spectrum of JHS/EDS-HT and the distinction between asymptomatic/"benign" gJHM and JHS/EDS-HT is often difficult especially within the same family; (2) many studies investigating the association between gJHM and GI features do not declare a formal exclusion of JHS/EDS-HT in their cohorts; (3) with the exception, perhaps, of vascular manifestations and spontaneous rupture of the gut which are typical of vascular EDS, all other GI manifestations seem shared by most EDS subtypes; (4) JHS/EDS-HT is probably the most common EDS subtype. Single case reports were also selected. For these works, the likelihood of the diagnosis of JHS/EDS-HT was ascertained by checking for a formal attribution of EDS subtype (i.e., JHS, EDS-HT, EDS type III) by the authors themselves, or by comparing the reported extra-GI manifestations with the Villefranche and Brighton criteria. The presence of spontaneous bowel rupture and/or suspected vascular accidents lead to the attribution of vascular EDS and, then, to exclude the paper.

RESULTS

Studies Associating Generalized Joint Hypermobility With Gastrointestinal Complaints

A total of 16 papers, all published in the last 18 years (1987–2014), were identified. Fifteen studies compared the rate of specific GI features with gJHM in two populations. In one of these fifteen studies [Arunkalaivanan et al., 2009], controls' data were extracted by previously published works [Nelson et al., 1995]. Twelve out of fifteen (80.0%) studies yielded positive results which were summarized in Table I. The remaining three failed to demonstrate an association between gJHM and specific GI features, in particular pelvic prolapse [Brækken et al., 2009; Hafizi et al., 2013; Derpapas et al., 2014]. More specifically, Brækken et al. [2009] did not identify a relationship between gJHM measured with the Beighton score (with a cut-off of $\geq$4) and pelvic organ prolapse comparing 49 women with 49 controls. Conversely, they found an association between pelvic organ prolapse and other "soft" markers, such as easy bruising and varicose veins, of an underlying connective tissue disorder ($P = 0.001$ and 0.005, respectively). Hafizi et al. [2013] compared positive Beighon score (with a cut-off of $\geq$4) with pelvic organ prolapse between patients' and controls' groups each composed of 60 adult females. Derpapas

TABLE I. Studies Investigating the Association Between (Unclassified/Nonsyndromic) Generalized Joint Hypermobility and Gastrointestinal Features

Reference[a]	gJHM assessing strategy	No. of patients	No. of controls	Characteristics of patients	Characteristics of controls	Investigated feature(s)	Rate in patients	Rate in controls	*P* value	Summary
Marshman et al., 1987	Measuring fifth finger extension with a specific finger goniometer	25	25	4 females and 21 males (6–93 years) who undergone surgery for complete rectal prolapse	4 females and 21 males (mean 67 years) admitted for surgery but without rectal prolapse	Fifth finger extension	81 ± 2.2 degrees	68 ± 1.7 degrees	0.001	Fifth finger is more extensible in patients who undergone surgery repair for rectal prolapse
Norton et al., 1995	2 or more of the following: 1) passive opposition of thumb (s) to the wrist, 2) passive hyperextension of fifth digit (s) to greater than 55°, 3) active hyperextension of elbow (s) to greater than 190°	39	69	Females (49–57 years) with gJHM	Females (51–59 years) without gJHM	Rectocele (any grade)	84%	48%	0.0002	Rectocele is more common and severe in females with gJHM
						Rectocele (grades 2 and 3)	34%	13%	0.009	
Pulliam and Schuster, 1995	Opposition of thumb to wrist, TMJ dysfunction, scoliosis	43	1566	39 females and 4 males (18–62 years) with chronic intestinal pseudoobstruction	Unselected individuals with GI symptoms	gJHM	46.5%	13.9%	<0.001	gJHM is more common in patients with chronic intestinal pseudoobstruction
Al-Rawi et al., 2004	Beighton score (≥4)	50	50	28 men and 22 women with hiatus hernia at endoscopy	30 men and 20 women with normal endoscopy	gJHM	22%	6%	0.001	gJHM is more common in adults with *hiatus* hernia
Jha et al., 2007	Beighton score (>4)	30	30	Females (20–58 years) with gJHM attending rheumatologic	Females (22–56 years) without gJHM attending a	Anal incontinence	23%	0%	0.01	Anal incontinence is more common in females with gJHM

TABLE I. (*Continued*)

Reference[a]	gJHM assessing strategy	No. of patients	No. of controls	Characteristics of patients	Characteristics of controls	Investigated feature(s)	Rate in patients	Rate in controls	*P* value	Summary
				clinic; Caucasians, Asian, Afrocaribbean	rheumatologic clinic; Caucasians, Asian, Afrocaribbean					
Reilly et al., 2008	Beighton score (>4)	39	41	13 females and 26 males (7–17 years) with slow transit constipation	18 females and 23 males (7–17 years) without constipation requiring medical treatment	gJHM (males)	38%	4%	0.004	gJHM is selectively more common in males with slow transit constipation
Arunkalaivanan et al., 2009	Beighton score (>4)	148	NA	Adult females with gJHM members of the Hypermobility Syndrome Association; Caucasians (98%)	General adult population; previously published data[c]	Faecal incontinence	14.9%	2.2%	<0.05	Faecal incontinence is more common in females with gJHM
Vounotrypidis et al., 2009	Beighton score; Brighton criteria for JHS	69	67	32 females and 37 males (18–50 years) with inflammatory bowel disease; Greek Caucasians	29 females and 38 males (18–50 years); Greek Caucasians	gJHM[b]	70.3% (Crohn disease)	25.4%	<0.0001	gJHM is more common in patients with Crohn disease; the chance of having Crohn disease among patients with inflammatory bowel disease and gJHM is twofold than ulcerative colitis
Mohammed et al., 2010	5-point questionnaire[d]	65	135	63 females and 2 males (15–80 years) with gJHM and intractable constipation	116 females and 19 males (20–83 years) with intractable constipation and without	Gender (female/male) Previous surgery for pelvic organ	96.9%/ 3.1% 30.7%	85.9%/ 14.1% 17.0%	0.02 0.04	Individuals with gJHM and chronic constipation are more commonly females with a history of surgery for pelvic prolapse and more commonly display

TABLE I. (*Continued*)

Reference[a]	gJHM assessing strategy	No. of patients	No. of controls	Characteristics of patients	Characteristics of controls	Investigated feature(s)	Rate in patients	Rate in controls	*P* value	Summary
					gJHM	prolapse				
						Incomplete rectal evacuation	80%	59%	0.004	incomplete rectal evacuation, functional rectocele and extrinsic compression of the anterior rectal wall at anorectal physiological investigation than patients without gJHM. The absence of a precipitating event for constipation is more common in the former group.
						Functional rectocele	58%	39%	0.01	
						Extrinsic compression of the anterior rectal wall	11	1	0.006	
Zarate et al., 2010	Beighton score (>4)	63	66	54 females and 9 males (16–71 years) with gJHM and unexplained GI symptoms	43 females and 23 males (18–78 years) without gJHM and unexplained GI symptoms	Known etiology	19%	59%	<0.0001	Individuals with gJHM and unexplained GI symptoms are younger, more frequently females, and more commonly display gastroesophageal reflux and bloating than patients without gJHM. Etiology of symptoms in gJHM patients is more commonly unknown than for individuals without gJHM.
						Age	37 years (mean)	44 years (mean)	0.01	
						Gender (female)	86%	65%	0.008	
						Gastroesophageal reflux	56%	30%	0.005	
						Bloating	62%	46%	0.05	
Lammers et al., 2012	"Presence of a luxation or spain of a joint"	110	100	Females (51–89 years) with gJHM attending gynecologic clinic	Females (51–95 years) without gJHM attending gynecologic clinic	Pelvic organ prolapse	19%	2%	<0.01	Pelvic organ prolapse is more common in females with gJHM
Kajbafzadeh et al., 2014	Beighton score (≥4)	113	113	Children (5–14 years) with voiding dysfunction;	Healthy schoolchildren (5–14 years); Iranians	gJHM (total)	45%	17%	0.001	gJHM is more common in children with voiding dysfunction. Among children with gJHM,
						gJHM (females)	44%	23%	0.017	

TABLE I. (*Continued*)

Reference[a]	gJHM assessing strategy	No. of patients	No. of controls	Characteristics of patients	Characteristics of controls	Investigated feature(s)	Rate in patients	Rate in controls	*P* value	Summary
				Iranians		gJHM (males)	34%	5%	0.04	urinary tract infections are more common in females, while constipation is more common in males

GI, gastrointestinal; gJHM, generalized joint hypermobility; JHS, joint hypermobility syndrome; NA, not available; TMJ, temporomandibular joint.
[a]Only features with statistically significant differences between patients' and controls' groups are reported in the table (i. e., *P* value <0.05).
[b]5 out of 29 individuals with gJHM and Crohn disease and 1 out of 10 individuals with gJHM and ulcerative colitis also met Brighton criteria for joint hypermobility syndrome with a cumulative OR of 3.75.
[c]From Nelson et al. [1995].
[d]The 5-point questionnaire is a self-reported questionnaire investigating historical gJHM [Hakim and Grahame, 2003].

et al. [2014] studied 270 women with urinary incontinence and pelvic organ prolapse, who were screening for gJHM with the self-reported 5-point questionnaire by Hakim and Grahame [2003].

Of the 12 studies with positive results (Table I), four studied adult females only [Norton et al., 1995; Jha et al., 2007; Arunkalaivanan et al., 2009; Lammers et al., 2012], five adult males and females [Pulliam and Schuster, 1995; Al-Rawi et al., 2004; Reilly et al., 2008; Vounotrypidis et al., 2009; Zarate et al., 2010], two children and adolescents from both sexes [Mohammed et al., 2010; Kajbafzadeh et al., 2014], and one children, adolescents and adults from both sexes [Marshman et al., 1987]. These works differed also for the assessing method for gJHM, which was the Beighton score with a positive cut-off of >4 four times [Jha et al., 2007; Reilly et al., 2008; Arunkalaivanan et al., 2009; Zarate et al., 2010], Beighton score with a positive cut-off of ≥ 4 twice [Al-Rawi et al., 2004; Kajbafzadeh et al., 2014], Beighton score with an undefined positive cut-off once [Vounotrypidis et al., 2009], the self-reported 5-point questionnaire once [Mohammed et al., 2010], and a self-developed screening method four times [Marshman et al., 1987; Norton et al., 1995; Pulliam and Schuster, 1995; Lammers et al., 2012]. Association between gJHM and chronic constipation, alternatively termed as chronic intestinal pseudoobstruction [Pulliam and Schuster, 1995] or slow transit constipation [Mohammed et al., 2010], appeared the most consistent, being observed four times in both sexes from all ages [Pulliam and Schuster, 1995; Reilly et al., 2008; Mohammed et al., 2010; Kajbafzadeh et al., 2014]. Also the link between gJHM with rectal/pelvic prolapse and anal/fecal incontinence seemed strong in women [Marshman et al., 1987; Norton et al., 1995; Jha et al., 2007; Arunkalaivanan et al., 2009; Lammers et al., 2012]. A study pointed out a relationship between constipation and a past history of pelvic prolapse in females [Mohammed et al., 2010]. Three further works highlighted the association between gJHM with some upper GI

TABLE II. Prevalence of Selected Gastrointestinal Features in Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type

Feature	Castori et al., 2010	Castori et al., 2011a					Zarate et al., 2010
No. of patients	21	50					21
		0–10 years	11–20 years	21–30 years	31–40 years	>40 years	
Dysphagia	—	—	—	—	—	—	14.3%
Dyspepsia/chronic gastritis	66.7%	8%	28%	40%	44%	48%	14.3%
Gastro-esophageal reflux	57.1%	20%	48%	60%	70%	74%	52.4%
Bloating	—	—	—	—	—	—	57.1%
Nausea	—	—	—	—	—	—	57.1%
Vomiting	—	—	—	—	—	—	57.1%
Recurrent abdominal pain	61.9%	26%	40%	54%	64%	68%	85.7%
Constipation/diarrhea	33.3%	54%	60%	70%	70%	72%	76.2%
Abdominal hernia(s)	4.8%	10%	14%	18%	18%	20%	—
Abnormal esophageal manometry	—	—	—	—	—	—	33.3%[a]
Abnormal 24 h pH-metry	—	—	—	—	—	—	33.3%[b]
Delayed gastric emptying	—	—	—	—	—	—	80%[c]
Abnormal small bowel manometry	—	—	—	—	—	—	44.4%[d]
Abnormal colorectal transit	—	—	—	—	—	—	100%[e]

[a]From a total of 12 patients, and including hypotonic lower esophageal sphincter (#1), ineffective esophageal motility (#2), and poor peristalsis of the lower esophagus (#1).

[b]From a total of 12 patients, and including mild reflux (#2) and pathologic reflux (#2).

[c]From a total of 15 patients.

[d]From a total of 9 patients, and including bursts of contractions (#2), loss of circadian cycles of motility (#2), absent nocturnal migrating motor complex (#1), no postprandial changes (#1), poor amplitude contractions (#1), retroperistalsis in the phase III of the migrating motor complex (#1), and lack of feeding pattern (#1).

[e]From a total of 6 patients, and including delayed colonic transit (#3), rectal hypersensitivity (#1), rectocele (#1), poor evacuatory effort (#1), rectal evacuatory disorder (#1), and circumferential intussusceptions (#1).

complaints (i.e., gastro-esophageal reflux and bloating) [Zarate et al., 2010], hiatus hernia [Al-Rawi et al., 2004], and Crohn disease [Vounotrypidis et al., 2009]. "Functional" nature of constipation and upper GI complaints in individuals with gJHM was envisaged twice by the net prevalence of an absent precipitating factor for both features in these subjects [Mohammed et al., 2010; Zarate et al., 2010]. A further, not tabulated paper analyzed the prevalence of specific anamnestic features in 568 women at 12 months postpartum after a high risk delivery (i.e., instrumental delivery and/or high birthweight infant), and found a relationship between fecal incontinence and gJHM in the patients' group [Chiarelli et al., 2003].

Studies Investigating Gastrointestinal Manifestations in JHS/EDS-HT

Concerning GI manifestations in JHS/EDS-HT, identified articles were subdivided in three groups: (1) works showing rough rates of selected GI features in JHS/EDS-HT [Hakim and Grahame, 2004; Castori et al., 2010, 2011a, 2012a; Zarate et al., 2010], (2) works comparing rates of selected GI features between JHS/EDS-HT and general population [Manning et al., 2003; Danese et al., 2011; Mastoroudes et al., 2013; Fikree et al., 2014], and (3) studies investigating the intra-phenotypic variability and scrutinizing the relationship of GI features with other manifestations/characteristics of JHS/EDS-HT [De Wandele et al., 2013; De Wandele et al., 2014; Pacey et al., 2014].

Group 1 consisted of five works. Hakim and Grahame [2004] first noted GI complaints in 37% of 170 women aged from 18 to 65 years. In this study, the value was cumulative for nausea, stomach ache, diarrhea and constipation, and separated rates were not available. By describing obstetric and gynecologic findings in 82 women with JHS/EDS-HT, we found GI complaints in 71.9% and rectal prolapse in 11.1% of cases [Castori et al., 2012a]. Three further works reported values by selected features and were summarized in Table II. While we described patient-

TABLE III. Studies Investigating the Association Between Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type and Gastrointestinal Features

Reference[a]	JHS/EDS-HT assessing strategy	No. of patients	No. of controls	Characteristics of patients	Characteristics of controls	Investigated GI feature(s)	Rate in patients	Rate in controls	*P* value	Summary
Manning et al., 2003	Modified Brighton criteria	404	397	Women with LUTD and obstructed defecation	Women with LUTD and without obstructed defecation	JHS "features"	70.6%	50.0%	<0.0001	JHS seems more common in women with LUTD and obstructed defecation than in those without defecatory problems; vice versa, defecatory problems are more common in women with LUTD and JHS than in those with LUTD but without JHS
		499	339	Women with LUTD and JHS	Women with LUTD and without JHS	Childhood constipation	7.7%	3.2%	0.01	
						Frequent loose stools	29.5%	22.6%	0.03	
						Frequent hard stools	36.7%	25.0%	0.0005	
						Frequent hard and loose stools	8.8%	4.9%	0.04	
Danese et al., 2011	Villefranche and Brighton criteria	31	NA	25 females and 6 males (years) with JHS/EDS-HT attending clinical genetics clinic	Italian general population; previously published data[b]	Celiac disease (Marsh classification)	16.1%	1.0%	0.002	Celiac disease is more common in JHS/EDS-HT
Mastoroudes et al., 2013	Brighton criteria	60	60	Females (18–60 years) with JHS attending hypermobility clinic	Females (18–60 years) without JHS recruited from hospital staff	Vaginal bulge interfering defecation	23.0%	5.0%	0.007	Defecatory problems are more common in females with JHS; there is a significant correlation between defecatory problems and posterior compartment prolapse in JHS females
						Straining for defecation	61.7%	NA	<0.001	
						Incomplete emptying after defecation	63%	NA	0.001	
						Need of digitation for defecation	33.3%	NA	<0.001	
Fikree et al., 2014	Brighton criteria	180	372	123 females and 57 males with JHS	203 females and 169 males without JHS	Age (mean)	40.6 years	44.2 years	0.003	JHS patients with GI symptoms are younger and more commonly females
						Gender (female)	68.3%	54.6%	0.002	

(*Continued*)

TABLE III. (*Continued*)

Reference[a]	JHS/EDS-HT assessing strategy	No. of patients	No. of controls	Characteristics of patients	Characteristics of controls	Investigated GI feature(s)	Rate in patients	Rate in controls	*P* value	Summary
				attending gastroenterologic clinic	attending gastroenterologic clinic	Heartburn	33.0%	23.5%	0.01	than non-JHS patients;
						Water brash	30.9%	18.5%	0.001	heartburn, water brash and
						Postprandial fullness	41.4%	27.1%	0.006	post-prandial fullness are more common in JHS patients; JHS patients with GI symptoms have more commonly extra-GI autonomic symptoms, fibromyalgia and chronic pain than non-JHS patients; JHS patients attending rheumatologic clinic feel worse than JHS patients attending gastroenterologic clinic.

EDS-HT, Ehlers–Danlos syndrome, hypermobility type; GI, gastrointestinal; JHS, joint hypermobility syndrome; LUTD, lower urinary tract disfunction; NA, not available.
[a]Only features with statistically significant differences between patients' and controls' groups are reported in the table (i. e., *P* value <0.05).
[b]From Menardo et al. [2006] and Dubé et al. [2005].

reported symptoms only [Castori et al., 2010, 2011a], Zarate et al. [2010] offered details on a series of GI physiology investigations including esophageal manometry, 24 hr pH-metry, gastric emptying study, small bowel manometry, and colorectal physiology study. In addition to the high rate of most GI complaints, the last work demonstrated a widespread dysfunction of the gut from the lower esophagus to the anus.

Group 2 comprised four works summarized in Table III. In the paper by Manning et al. [2003], women with lower urinary tract dysfunction were investigated for clustering of specific features and a clear relationship between JHS/EDS-HT and defecatory problems emerged in this patients' subgroup. Danese et al. [2011] reported a small study suggesting a relationship between celiac disease and JHS/EDS-HT comparing data between 31 JHS/EDS-HT patients of both sexes and with various ages, to previously published data on rate of celiac disease in the general population [Dubé et al., 2005; Menardo et al., 2006]. Mastoroudes et al. [2013] demonstrated a significant excess of various defecatory problems in 60 JHS/EDS-HT women compared to highly matched controls. The largest study is that by Fikree et al. [2014] on 187 JHS/EDS-HT adults compared to 372 controls, all attending a gastroenterologic clinics. In this work, JHS/EDS-HT patients resulted more commonly females and younger than controls and tended to display more commonly several upper GI complaints. An association of extra-GI autonomic complaints, fibromyalgia, and chronic pain with JHS/EDS-HT was also confirmed.

Group 3 included three papers. In one paper, De Wandele et al. [2013] carried out a multiple questionnaire study on 78 JHS/EDS-HT adults (70 women and 8 men) screened for the Villefranche criteria, with the aim of investigating feature clustering. Three clusters were identified and GI complaints resulted more common in cluster 2, which showed the highest rate of fatigue, sleeping disorders, orthostatic

intolerance, thermoregulatory problems, inflammatory signs and cardiovascular symptoms, as well as the largest functional impairment and the most severe pain. In a further work, the same research group from Ghent (Belgium) compared the rate and impact on quality of life of selected "autonomic" complaints in 80 adults with JHS/EDS-HT in comparison with 11 individuals with classic EDS, 7 with vascular EDS, 38 with fibromyalgia and 43 controls. Among the EDS groups, JHS/EDS-HT patients showed the highest rate of autonomic features, and the burden was higher than other EDS patients and comparable with the fibromyalgia group. In this study, selected GI complaints included gastroparesis (registered in 58 JHS/EDS-HT patients), constipation (53 patients) and diarrhea (51 patients) [De Wandele et al., 2014]. Pacey et al. [2014] presented the results of a questionnaire study in 89 children with the Brighton criteria for JHS. Analysis of data identified five clusters and one of them (called "systemic JHS") was characterized by the unique symptoms of skin involvement and urinary stress incontinence, as well as a high rate of recurrent joint instability and GI involvement. GI involvement was defined by the presence of recurrent constipation, diarrhea or abdominal pain, or the diagnosis of slow transit constipation or irritable bowel syndrome. No further detail was offered on these features.

Surgical Reports in JHS/EDS-HT

Fifteen case reports describe surgical techniques (and their outcomes) for various GI problems in JHS/EDS-HT (Table IV). A definite diagnosis of JHS according to Brighton criteria or EDS-HT according to Villefranche criteria was declared in seven instances [de Weerd et al., 2012; Reinstein et al., 2012; Dordoni et al., 2013; Fogel, 2013; Sardeli et al., 2013; Plackett et al., 2014]. In six patients, the diagnosis of EDS remained unclassified in the original report, but JHS/EDS-HT was considered, retrospectively, the most likely based on the description of extra-GI features [Douglas and Douglas, 1973; Shaikh and Turner, 1988; Leung, 1989; Defuentes et al., 2004; Levine and Adler, 2005; Chen and Jao, 2007]. In two additional cases, the authors proposed the diagnosis of classic EDS but applied criteria did not satisfy available recommendations [Mayer et al., 2013]. In these cases, JHS/EDS-HT was considered more appropriate in the light of the described picture [Phadke, 1978; Pelizzo et al., 2013]. Summarizing data from available literature is difficult due to the extreme heterogeneity in clinical presentation, accuracy of EDS subtype definition and details on the long-term outcome. In JHS/EDS-HT, surgery appeared repeatedly successful for treating diaphragmatic defects leading to a variety of clinical presentations [Phadke, 1978; Shaikh and Turner, 1988; Leung, 1989; Levine and Adler, 2005]. In turn, surgery was uneffective multiple times for the correction of visceroptosis and pelvic organ prolapse [de Weerd et al., 2012; Dordoni et al., 2013; Pelizzo et al., 2013]. Laparoscopic subtotal colectomy for bowel ptosis had positive results in one instance [Reinstein et al., 2012], as well as the repair of a recto-vaginal fascia with porcine small intestinal submucosa mesh in a woman with pelvic organ discomfort for multiple prolapses [Sardeli et al., 2013]. The injection of 5 ml of 5% phenol in almond oil resulted effective in treating recurrent rectal prolapse in a 2-year-old infant [Douglas and Douglas, 1973].

Studies Investigating Gastrointestinal Manifestations in Patients' Cohorts With Unclassified EDS Subtypes

A handful of papers report large data on various GI aspects in EDS, but information cannot be extrapolated by clinical subtype. As JHS/EDS-HT is presumed to represent a proportion of EDS patients, except those presenting with acute symptoms due to spontaneous vessel or bowel rupture, in most studies, the main results of these works were equally summarized. An early work by Beighton et al. [1969] reported a retrospective study on GI complications in 125 EDS patients. Stratification was not available and vascular complications are likely related to the vascular subtype. However, in this work, the authors pointed out a not stochastic association between EDS and a series of GI and abdominal features, including diverticula at different points of the gut, rectal prolapse, and various abdominal and diaphragmatic hernias. A more recent study found swallowing difficulties in 39% of 411 EDS patients affected by the types I, II, III, IV, and VI (former classification) [Hunter et al., 1998]. Carley and Schaffer [2000], by reporting data on urinary incontinence and pelvic organ prolapse in 12 Marfan and 8 EDS women, described rectal prolapse in 2 (25%) EDS patients. More recently, Zeitoun et al. [2013] reported the results of a questionnaire study on 134 patients with various EDS subtypes (with a presumably high prevalence of JHS/EDS-HT) and found a high rate of symptoms of dyspepsia and gastroesophageal reflux, irritable bowel syndrome, and functional constipation. The Gastrointestinal Quality of Life index was significantly lower in the EDS cohort compared to controls. Based on their experience, the authors considered endoscopy of the upper gut relatively safe, while they were more sensitive in performing colonoscopy due to organ fragility in vascular EDS and the risk of mucosal bleeding in most EDS subtypes. Abonia et al. [2013] described a 8-fold risk of eosinophilic esophagitis in patients with hereditary connective tissue disorders compared to the general population. The genetic background of the connective tissue disorder group seemed heterogeneous with patients with EDS, Marfan and Loeys–Dietz syndromes. A peculiar *facies* in patients with the combination of connective tissue disorder and eosinophic esophagitis was also proposed.

DISCUSSION

In this review, we confirmed a strong relationship between a variety of GI disorders and JHS/EDS-HT. Given the relatively high frequency of this condition compared to other heritable

TABLE IV. Case Reports of Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type With Surgical Features Involving the Gut

Reference	EDS subtype	Age	Sex	Ascertainment	Main clinical feature(s)	GI symptom(s)	Anatomical finding/feature(s)	Surgery
Douglas and Douglas, 1973	Presumed EDS-HT	2 years	Unknown	Rectal prolapse	gJHM, "inelastic" skin	Recurrent rectal prolapse	Rectal prolapse	Effective treatment with the injection of 5 ml of 5% phenol in almond oil
Phadke, 1978	Presumed EDS-HT[a]	71 years	Female	Prolonged emesis	gJHM, osteoarthritis, kyphoscoliosis, skin hyperextensibility, poor wound healing, subcutaneous spheroids	Recurrent emesis	Eventration of left diaphragm and torsion of stomach	Effective repair of the diaphragmatic defect
Shaikh and Turner, 1988	Presumed EDS-HT	17 years	Female	Acute GI complaints	gJHM, dislocations, scoliosis	Epigastric pain, emesis and an history of generalized abdominal pain	Strangulation and infarction of the stomach through the diaphragm	Effective gastrectomy with pyloroplastic
Leung, 1989	Presumed EDS-HT	22 years	Male	Acute GI complaints	NA	Epigastric pain, emesis	Strangulation of the stomach	Effective repair of the diaphragmatic defect
Defuentes et al., 2004	Presumed EDS-HT	25 years	Female	GI complaints	gJHM, skin hyperextensibility, absent lingual and hypoplastic labial frenula	Abdominal pain with fever	Multiple diverticula of descendent and trasverse colon	None
Levine and Adler, 2005	Presumed EDS-HT	22 years	Female	Dyspnea, chest pain, emesis	gJHM, dislocations, fractures, poor wound healing, positive family history	Emesis after pharmacologic therapy for a dislocation	Rupture of diaphragm, paraesophageal hernia	Effective repair of the diaphragmatic defect and Nissen fundoplication
Chen and Jao, 2007	Presumed EDS-HT	20 years	Male	Defecation problems	gJHM, skin hyperextensibility, easy bruising, large rectal prolapse	Defecation problems	Rectal prolapse	Effective conservative treatment
Reinstein et al., 2012	EDS-HT	28 years	Female	GI complaints	gJHM, dislocations, soft skin, easy bruising, arachnodactyly, myopia	Disabling abdominal distension and bloating	Prolapse of the small bowel and transverse colon, increased bowel mobility under direct manipulation	Effective laparoscopic subtotal colectomy

TABLE IV. (*Continued*)

Reference	EDS subtype	Age	Sex	Ascertainment	Main clinical feature(s)	GI symptom(s)	Anatomical finding/feature(s)	Surgery
de Weerd et al., 2012	EDS-HT	47 years	Female	Defecation problems	NA	Incomplete evacuation, constipation, pelvic pain and discomfort	Hiatal hernia, anal mucosal prolapse, recto-anal intussusception, small rectocele and large enterocele	Abdominal plastic surgery, previous unsuccessful operation for anal prolapse and recto-anal intussusception, Nissen fundoplication, hysterectomy
Dordoni et al., 2013	JHS	38 years	Female	GI complaints	Beighton score 4/9, joint pain, skin hyperextensibility, *striae distensae*, delayed wound healing, blue sclerae, myopia	Dyspepsia and constipation	Prolapse of stomach, liver, small and large bowel, left kidney, ovaries	Recurrence after repeated gastropexy and nephropexy
	JHS	70 years	Male	Family study	Skin hyperextensibility, multiple dislocations, blue *sclerae*, obstructive lung disease	Irritable bowel syndrome	Mild prolapse of the small bowel, inguinal hernia	None
Fogel, 2013	EDS-HT	35 years	Female	Retrospective surgery study	Multiple knee dislocations which needed wheelchair, positive family history	NA	Multiple sepsis with microperforations of the colon, small bowel obstruction	Cholecystectomy, appendectomy, total abdominal colectomy and ileostomy, lysis of adhesions
Pelizzo et al., 2013	Presumed EDS-HT[a]	14 years	Female	Shock with abdominal distension and dehydration	NA	Chronic intestinal pseudo-obstruction symptoms	Dilatation of the ascending colon and terminal ileum	Recurrence after repeated ileostomy
Sardeli et al., 2013	EDS-HT	57 years	Female	Recurrence of defecation dysfunction	Joint and limb pain, patellar luxations, easy bruising	Inability to evacuate, constipation and mass sensation in the vagina	Rectocele	Successful correction of the defect in the recto-vaginal fascia with porcine small intestinal submucosa mesh

TABLE IV. (*Continued*)

Reference	EDS subtype	Age	Sex	Ascertainment	Main clinical feature(s)	GI symptom(s)	Anatomical finding/feature(s)	Surgery
Plackett et al., 2014	EDS-HT	34 years	Female	Bleeding hemorrhoids	gJHM, dislocations, back pain, skin hyperextensibility, easy bruising	Rectal bleeding	Hemorrhoids	Conservative treatment (outcome not available)

GI, gastrointestinal; EDS-HT, Ehlers–Danlos syndrome- hypermobility type; gJHM, generalized joint hypermobility; JHS, joint hypermobility syndrome.
[a]In these cases, the diagnosis of classic EDS was proposed by the authors with the sole presence of subcutaneous calcified spheroids in Phadnke [1978] and unreported "hallmarks of disturbed fibrillogenesis" at skin biopsy in Pelizzo et al. [2013].

connective tissue disorders, JHS/EDS-HT emerges as a model for studying the pathophysiologic basis of such an association and, reasonably, identifying more tailored management and treatment approaches. A great proportion of the reviewed studies investigated the link between apparently, non-syndromic gJHM and various GI manifestations. At the moment, whether their findings can be generalized to JHS/EDS-HT or not remains to be determined. However, these studies emphasize the relevance of raising the scientific interest in this field. In fact, accumulated evidence on the non-casual association between gJHM and many potentially disabling GI disorders opens us a novel approach for interpreting highly prevalent complaints in humans. Based on results of this review, the spectrum of GI manifestations in JHS/EDS-HT may be simplistically organized in structural and functional features. Available evidence concerning these two groups is summarized as follows.

Structural features:

(1) Abdominal hernias occur in up to one fifth of the patients, the chance of occurrence increases with age, and their surgical treatment seems effective under standard procedures.

(2) Rectal prolapse is observed in more than one tenth of women. It can occur in nulliparous women but its rate is highest in those who underwent episiotomy. As the chance of fecal incontinence as symptomatic surrogate of pelvic dysfunction associates with high-risk deliveries also in the general population, in JHS/EDS-HT pregnant women, it seems reasonable to recommend Cesarean as the first-choice delivery modality in order to prevent long-term disabilities in an affected mother. Treatment of symptomatic pelvic prolapse remains problematic in JHS/EDS-HT and surgery is generally not effective. There is a single report of rectal prolapse in a 2-year-old infant with presumed JHS/EDS-HT [Douglas and Douglas, 1973]. The rate of rectal prolapse in men and children with JHS/EDS-HT remains unknown.

(3) Ptosis of internal organs (Figs. 1 and 2), such as stomach, transverse colon and kidney is described in few clinical reports. Although apparently rare, renal, colonic, and gastric ptosis may be underestimated in JHS/EDS-HT and their manifestations may be influenced by position and gravity. Treatment by organopexis is generally unsuccessful and the link between such an anatomic feature and the presumably associated symptoms remains unclear in JHS/EDS-HT. Colonic reduction by laparoscopy resulted effective once.

(4) Diaphragmatic (e.g., *hiatus*) hernias and intestinal intussusceptions are likely additional structural manifestations of GI involvement in JHS/EDS-HT, but available data are too preliminary to affirm a non-casual relationship.

Functional manifestations:

(1) Collectively, the rate of functional GI symptoms is high, increases with age and ranges from ~1/3 to ~3/4 of the patients. Although GI manifestations are still not included in the available clinical criteria for JHS/EDS-HT, their frequency and related impact on quality of life suggest consideration of GI involvement as a major feature of this condition.

2) In JHS/EDS-HT, functional GI features span from mouth to anus and mainly includes dysphagia, gastroesophageal reflux, dyspepsia, irritable bowel disease, and chronic constipation. The typical adult patient presents with multiple, variably combined symptoms, while (isolated) chronic constipation is the most common manifestation in children.

3) Functional tests, including esophageal manometry, 24 hr pH-metry, gastric emptying study, small bowel manometry, and colorectal transity study, often lead to positive results but should be considered second-line investigations and performed in highly specialized settings, preferably by professionals with experience on JHS/EDS-HT. Swallowing studies could be also considered in patients with upper GI complaints but evidence is still lacking.

4) First-line investigations, such as upper GI endoscopy, could be performed safely, but usually lead to negative or inconsistent results. Colonoscopy should be performed with care due to a possibly increased risk of

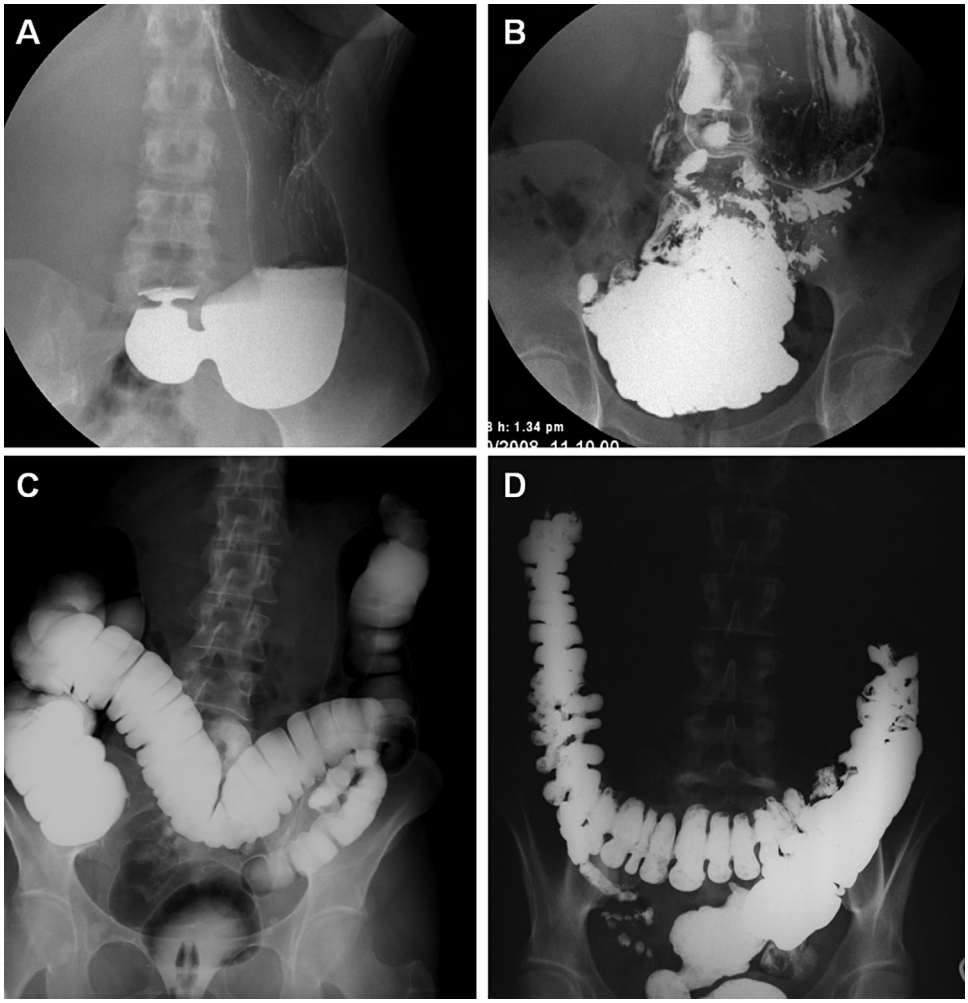

Figure 1. Ptosis of the gut in JHS/EDS-HT. Gastroptosis in a woman with JHS/EDS-HT who also displayed delayed gastric emptying at gastric emptying study (A). The same patient also showing dislocation of the small bowel in the pelvis (B). Different degrees of large bowel ptosis in orthostatism in adults with JHS/EDS-HT (C, D).

mucosal bleeding. Colonic redundancy, ptosis and/or hypermobility may be further limitations to colonoscopy.

5) Treatment of functional GI complaints in JHS/EDS-HT is problematic due to the absence of tailored strategies and an apparent resistance to pharmacologic treatments at standard dosages/regimens. The exclusion of common co-morbidities, such as celiac disease, lactose intolerance, and *Helicobacter pylori* infection, is reasonable at first examination.

6) Due to the lack of efficacious treatments and the absence of known precipitating triggers (perhaps, except for inadequate surgical treatment of internal and pelvic organ prolapse(s) as well as traumatic deliveries), patients' education, also comprising diet and nutritional advice, seems at the moment the most effective management tool.

Pathogenesis of GI manifestations in JHS/EDS-HT is still largely unknown and the existence of specific factors remains speculative. Recently, particular attention has been posed on dysautonomia as a major contributor to onset and/or progression of a wide spectrum of functional GI complaints in JHS/EDS-HT [Zarate et al., 2010; Castori et al., 2013b; De Wandele et al., 2013, 2014; Farmer et al., 2014]. The strength of this hypothesis, though promising, is actually hampered by the descriptive nature of published works and the objective difficulties encountered in investigating its underlying pathophysiology. Furthermore, in JHS/EDS-HT, the influence of dysautonomia is reasonably weaker for other GI manifestations, such as internal organ prolapse and mucosal bleeding.

More widely, connective tissue is strongly represented in various components of the GI *apparatus*, such as peritoneal ligaments, gut wall and splanchnic vessels. Peritoneal ligamentous laxity leading to hypermobility of the intra-abdominal viscera is considered a predisposing factor to abdominal twists and torsions [Timpone et al., 2011], and could facilitate visceral prolapse or hernias under the additive

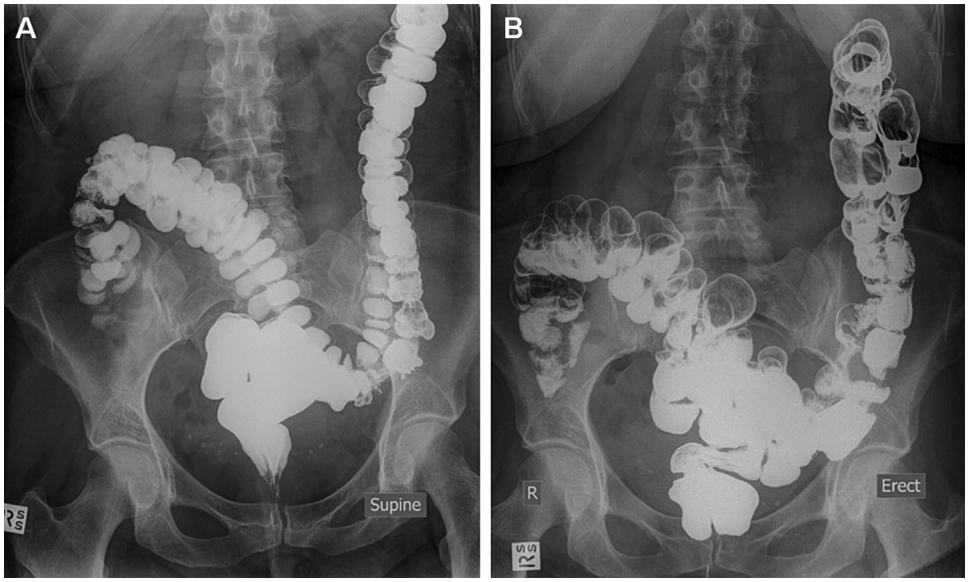

Figure 2. Contrast abdominal radiograph in an adult with JHS/EDS-HT. Comparison between the supine (A) and erect position (B). There is an overt downward dislocation of the entire colon, sigmoid, and rectum in orthostatism compared to clinostatism.

effect of orthostatism and other factors increasing intra-abdominal pressure (such as, pregnancy and chronic constipation). Accordingly, Curci et al. [2008] found subtle alterations of the elastic fibers in the supporting ligaments of the gastro-esophageal junction in patients with gastro-esophageal reflux and *hiatus* hernia.

An abnormal connective tissue content within the gut wall may affect its functions by increasing the compliance of hollow viscera with excessive distension, as well as by directly interfering with gut mechano-receptors embedded in the connective tissue-rich *muscularis externa* [Grundy and Schemann, 2006]. Summative effects of this process may include influences on pain thresholds and gut motility, both known contributors to various functional GI complaints, such as gastro-esophageal reflux, abdominal pain, bloating, diarrhea and constipation [Farmer and Aziz, 2014]. Furthermore, a defect of the extracellular matrix in the *lamina propria* and secondary alterations of luminal microbiota may affect permeability of gut mucosa, a mechanism which may explain, in part, the associations with celiac disease [Danese et al., 2011], Crohn disease [Vounotrypidis et al., 2009] and eosinophilic esophagitis [Abonia et al., 2013].

Capillary fragility is a well-known cutaneous and oral manifestation of JHS/EDS-HT [Castori et al., 2015]. Although accurate data are lacking, an extension of this feature to the entire GI mucosa is reasonable and may explain a presumed propensity to minor hemorrhages. A reduced capillary and small vessels resilience may also contribute to peripheral blood steal, which may exacerbate various autonomic manifestations, such as nausea and bloating. Finally, reduced vascular resilience to external forces may exacerbate the transitory effects of mesenteric tractions and compressions on peripheral blood supply, which, in turn, is related to peritoneal ligamentous hypermobility.

Finally, literature review emphasized the role of GI complaints on quality of life of JHS/EDS-HT patients. Comparably to musculoskeletal pain and fatigue [Voermans and Knoop, 2011], GI manifestations should be considered major contributors to disability in JHS/EDS-HT. However, the scarce knowledge of their pathophysiologic basis explains why surgery and standard pharmacologic treatments are usually of minor effect at the long-term, with great frustration for patients and practitioners. Hence, in the ensuing years, clinical research should be focused on: (1) identifying reliable and standardized procedures for assessing the role of the various pathogenic contributors to the resulting GI disability in any given patient; (2) moving towards a multidisciplinary management of GI disability in JHS/EDS-HT with a more active involvement of nutritionists, physiotherapists, pelvic floor specialists, and non-traditional medicine practitioners; (3) making up prevention programs to be applied in order to counteract the downward spiral of GI disability, and based on tailored lifestyle interventions and diet education. Concerning the latter, the following section is dedicated to reasonable nutriceutical interventions in JHS/EDS-HT.

NUTRITIONAL ASPECTS

Background

The role of nutritional therapy in EDS and, in particular, in JHS/EDS-HT is, at the moment, purely speculative. In 2005, Mantle et al. listed a series of dietary supplements and nutraceuticals

potentially beneficial for improving some EDS features. Among these supplementations, there are carnitine, co-enzyme Q10, vitamin C, and various chondral protectors, which could be easily prescribed for both preventive and therapeutic issues. Accordingly, Tinkle [2010] reported his experience with selected nutraceuticals in JHS/EDS-HT.

The role of diet in symptom onset and progression in JHS/EDS-HT may extend much beyond the biochemical counteract of single pathogenic processes in the postnatal life. The understanding of epigenetic effects of dietary supplementations in both health and disease in humans is in its infancy. Nevertheless, a couple of papers in the field of gJHM put the basis for possible future studies. In particular, Hasija and et al. [2008] demonstrate a direct relationship between degree of generalized gJHM and nutritional status in Indian children. This study envisages that a healthy and balanced diet may improve the range of joint motion also in the symptomatic pediatric patient, with or without a pre-existing diagnosis of EDS. De Felice et al. [2007] focused on 77 children born with intrauterine growth retardation and identified a subgroup of patients characterized by higher head circumference and an increased rate of bilaterally nonfunctional posterior communicating arteries, peculiar external ear morphology and otoacustic emissions, soft skin and gJHM. Follow-up observations show that some of these features, including ear morphology, otoacustic emission pattern and bilaterally nonfunctional posterior communicating arteries, are also present in the patients' mothers, and that this subgroup of children associates with a lower rate of maternal induced hypertension/pre-eclampsia during pregnancy.

These findings introduce the concept that, in selected subjects/families, generalized gJHM could associate or be a consequence of a "primary" form of intrauterine growth restriction and that a series of apparently unrelated features can be traced along the maternal side. The link between growth restriction and gJHM remains unexplained, but if it exists it probably lies on the adequacy of intrauterine nourishment to the embryo/fetus. On this perspective, gJHM and, possibly, various associated features seem to be strongly influenced by diet and, then, it is reasonable that they are efficiently managed/improved by *ad hoc* nutritional supplementations.

Given such a unsolved gap of knowledge, we simplistically fragmented the disability of JHS/EDS-HT in five domains, including osteoarticular manifestations, musculoskeletal pain, poor sleep quality and fatigue, skin and mucosal features, and GI manifestations, in order to discuss the possible application of nutritional supplementations in the long-term management of this condition. All the following considerations should be considered low-level recommendations exclusively based on the authors' experience and speculations. This section of paper is inspired by a book chapter recently published by the authors on the same topic [Castori et al., 2014].

Osteoarticular Features

Whether gJHM predisposes to or rather protects from premature osteoarthritis is still a matter of debate [Jónsson et al., 2009]. Most publications are focused on unselected individuals ascertained for the presence/absence of gJHM. With this approach, personalization of data by phenotypic subgroup (e.g., JHS/EDS-HT) is lost. Nevertheless, while in the general population the link between congenital laxity of joints and premature joint damage is unclear, in subjects with JHS/EDS-HT this association seem likely [Castori et al., 2013a]. Recurrent joint macro- and microtraumatisms are more common in patients with JHS/EDS-HT. The ensuing early and polyarticular chondral damage is probably one of the very first steps acting in the evolution of musculoskeletal pain in JHS/EDS-HT. Improved joint stability may be attained by regular physical activity aimed at improving muscle tone and proprioception. However, the preventing and, hopefully, therapeutic effect of this general recommendation could be amplified by specific nutritional interventions. An extensive review is available describing actual nutritional resources for osteoarthritis in general population [Lopez, 2012ab]. Among those accounting data in support to safeness and beneficial effects on osteoarthritis, there are: eicosapentaenoic + decosahexaenoic acid (polyunsaturated fatty acids - PUFA) 2–4 g/day, γ-linolenic acid 0.5–2 g/day, glucosamine 2 mg/kg/day, chondroitin 1.2 g/die, hyaluronan 50–100 mg/day, avocado-saybean saponifiable fraction (ASU) 300–600 mg/day, S-adenosylmethionine 400–600 mg twice/day, MSM (an organic sulfur donor nutrient) 1–3 g twice/day, phytoflavonoids/polyphenols 150–1,000 mg twice/day, probiotics/prebiotics 1–6 billion CFU/day, vitamin C 250 mg twice/day, vitamin E 200 IU/day, vitamin D3 1,000–4,000 IU/day, vitamin K2 0.5–1 mg/day, selenium 200–400 μg/day, manganese 5–10 mg/day, boron 6–8 mg/day and zinc 25–50 mg/day, as well as undenatured type II collagen (40 mg/day) [Lugo et al., 2013].

Reduced bone mass is a further osteoarticular feature which is commonly encountered in JHS/EDS-HT [Dolan et al., 1998; Gulbahar et al., 2003]. Therefore, in JHS/EDS-HT patients a preventive therapy with vitamin D3 is envisaged. In the absence of *ad hoc* prescriptions, the JHS/EDS-HT patient should follow the schedule of the recommended dietary allowance of vitamin D (e.g., 400 IU/day up for the first year of life, 600 IU/day up to 70 years and 800 IU/day over 70 years). Higher dosages of vitamin D3 (e.g., 880 IU/day for adults) are recommended in case of demonstrated reduced bone mass. As JHS/EDS-HT patients could suffer of various forms of GI dysfuction, dosage of serum vitamin D3 and calcium levels may be useful particularly at the beginning of dietary supplementation.

Musculoskeletal Pain

Pain is a major disability contributor in JHS/EDS-HT [Voermans and Knoop, 2011]. Its pathogenesis remains not

well understood. Nevertheless, observational data on large patients' samples help in tracing the natural history of pain in JHS/EDS-HT [Castori et al., 2010, 2011a, 2013a]. In light of these recent advances, it is presumed that different pathogenic mechanisms contribute to the perceived pain at different disease phases. In the first phase, pain is likely related to joint damage. Hence, delay in the onset of precocious osteoarthritis could result in a delay in recurrent/chronic painful perceptions.

In more advanced disease phase, pain tends to chronification and this change is usually marked/accompanied by neuropathic symptoms. Again, many of the previously cited nutraceuticals, such as PUFAs and phytoflavonoids/polyphenols, with beneficial effects on joint health may mitigate painful sensations via a contra-inflammatory effect. With the onset of neuropathic pain [Camerota et al., 2010], the repertoire of nutriceutical supplementations may be expanded to other supplementations recently tested in common painful conditions also frequently reported in JHS/EDS-HT. In particular, magnesium therapy, consisting in a 2-week daily intravenous administration of magnesium solphate 1 g followed by a 4-week oral administration of magnesium oxide 400 mg and magnesium gluconate 100 mg, has been recently demonstrated effective in a double-blinded randomized controlled study in chronic back pain with a neuropathic component [Yousef and Al-deeb, 2013]. Vitamins B are further dietary supplementations with potential usefulness in controlling chronic pain [Sesti et al., 2011]. For example, a recent work highlights the improvement of the analgesic effect of diclofenac by supplementations with thiamine (vitamin B1) 100 mg, pyridoxine (vitamin B6) 100 mg and cyanocobalamin (vitamin B12) 5 mg in patients with osteoarthritis [Magaña-Villa et al., 2013]. Such a strategy may be considered in JHS/EDS-HT, especially in presence of early osteoarthritis.

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide which, through modulation of mast cells and spinal glial cells activation on peripheral and central nervous system neurons, has been demonstrated effective on the different inflammatory mechanisms that develop and maintain both neurogenic and neurophatic pain [Keppel Hesselink, 2012]. Clinical practice is experiencing an increasing body of evidence supporting the successfulness of its application [Keppel Hesselink and Hekker, 2012]. PEA is classified as a food for medical purposes or as a diet supplement in various countries of Europe. With a standard dose of 600 mg twice/day (with possibility of reduction to 300 mg twice/day), it may be used as a dietary supplementation with potentially beneficial effects on pain, especially of neuropathic origin. As data on the effects of a long-lasting dietary supplementation by PEA are still lacking, prudence suggests parsimonious use limited to periods of exacerbation of symptoms in JHS/EDS-HT.

Poor Sleep Quality and Fatigue

Quality of sleep is generally poor in EDSs [Verbraecken et al., 2001; Voermans et al., 2010a] and possible causes include periodic limb movements and nocturnal musculoskeletal pain [Verbraecken et al., 2001; Voermans et al., 2010b]. Although true sleep apnea seems relatively rare in EDSs [Verbraecken et al., 2001], a recent paper reporting results of polysomnography in 34 EDS patients demonstrates flow limitation, apneas and hypopneas with a decrease in flow limitation and an increase of apnea and hypopnea events with age [Guilleminault et al., 2013]. Treatment of the prevalent symptom/mechanism, if any, is indicated along with adherence to standard recommendations of sleep hygiene (consultable at: yoursleep.aasmnet.org/Hygiene.aspx).
In addition to dietary supplementations possibly beneficial for musculoskeletal pain, melatonine is commonly prescribed in JHS/EDS-HT at standard dosage [Tinkle, 2010].

Mechanisms leading to chronic fatigue in JHS/EDS-HT, are obscure and specific treatments are lacking. Possible major contributors include poor postural control, nocturnal pain and cardiovascular dysautonomia [Castori et al., 2013a]. Various papers highlight the common co-morbidity with chronic fatigue syndrome and fibromyalgia [Oflouglu et al., 2006; Castori et al., 2011b]. These association studies point out the possibility of a common pathogenesis which could lay in a secondary mitochondrial dysfunction [Smits et al., 2011]. Accordingly, the JHS/EDS-HT-associated fatigue may be managed with dietary supplementations used in various mitochondrial dysfunctions [Nicolson, 2013]. A combination of oral supplements, which resulted efficacious in treating chronic fatigue in patients with a variety of diagnoses, includes membrane phospholipids 2,000 mg/day, co-enzyme Q10 35 mg/day, microencapsulated reduced nicotinamide adenine dinucleotide (NADH) 35 mg/day, L-carnitin 160 mg/day, and α-ketoglutaric acid 180 mg/day [Nicolson et al., 2012a,b]. In the previous review on nutritional supplementations in EDS, Mantle et al. suggested a 100 mg daily dose of coenzyme Q10 and a 250 mg daily dose of carnitin. Recent speculations indicate a higher efficacy of the acetyl-L-carnitin derivative in treating symptoms of central origin [Malaguarnera, 2012], such as fatigue.

Skin and Mucosal Manifestations

Skin and mucosal fragility is a feature of JHS/EDS-HT. Easy bruising, delayed wound healing, recurrent gingival hemorrhages after tooth brushing and proneness to gingival retractions are all commonly reported. It is well established that vitamin C is necessary for wound healing, as naturally demonstrated by the adverse effects of vitamin C deficiency in selective malnutrition ("scurvy"). In fact, vitamin C is a cofactor of lysyl- and prolyl-hydroxylases, which stabilize the triple-helical structure of collagen and, if mutated, can cause various heritable connective tissue disorders, such as kyphoscoliotic type of EDS. A dose of 500–3,000 mg/day may be prescribed in JHS/EDS-HT.

Although literature is not clear, many JHS/EDS-HT patients refer a wide range of cutaneous features possibly related to impaired epithelial integrity, such as keratosis pilaris, xerosis, itching, eczema-like changes, and various skin allergies. As many of these findings are equally observed in scurvy, an adequate intake of vitamin C in JHS/EDS-HT could improve also these satellite features. Skin health may be improved by regular intake of many other dietary supplementations, including but not limited to vitamin E, polyphenols, coenzyme Q10, prebiotics/probiotics, and polyunsaturated fatty acids (vitamin F) [Schagen et al., 2012]. Regular assumption of these dietary supplementations by JHS/EDS-HT patients is supported by their simultaneous beneficial effect on joint protection (see previous section). Vitamin A is a further antioxidant with potential beneficial effect on skin health and integrity. Nevertheless, as it is a known teratogen and many JHS/EDS-HT patients, at the time of first evaluation, are young women, the use of vitamin A should not be recommended outside specific conditions, such as adult males and older women (i.e., vitamin A 0.8–1 mg/day = 2,400–3000 IU/day).

Mucosal dryness is a feature of JHS/EDS-HT and it causes various disabling features, such as xerophthalmia with positive Schirmer test [Gharbiya et al., 2012], xerostomia, and dyspaurenia and recurrent vaginal infections due to vaginal dryness. Adequate daily hydration (2–2.5 lt/day for adults) is a harmless dietary habit which may contribute in reducing symptom intensity. Beneficial effect on tear composition and dry eye may be also obtained by regular carnitin intake, as previously reported for fatigue [Flanagan et al., 2010], as well as vitamin A.

Gastrointestinal Manifestations

The first part of this paper highlights that GI functional complaints are extremely common in JHS/EDS-HT. Despite their high prevalence, disease-oriented treatment strategies are still lacking and available therapies have little impact on the long-term quality of life of affected individuals. In addition, common GI affections such as lactose intolerance, celiac disease, non-celiac glucose intolerance and opioid-drug overuse, not necessarily related to the underlying disorder may concur with JHS/EDS-HT. Therefore, adherence to appropriate dietary habits (appropriate number/fragmentation of meals, regular fiber intake, avoiding specific foods stimulating gastric secretion, and/or gut motility, etc) should be considered mandatory.

Among the various dietary supplementations with potential effects, probiotics and prebiotics are the sole for which experimental studies have been published, mostly in irritable bowel syndrome. Recent reviews of the literature [e.g., Whelan, 2011; Whelan and Quigley, 2013] indicate that, in irritable bowel syndrome, probiotics result effective in not all studies and that its effectiveness is mostly related to single symptoms rather than the entire GI phenotype. In addition, variability in the outcome is influenced by many factors, including microbiological characteristics of probiotics and "quality" of the industrial product used in the study. Therefore, the level of evidence for the efficacy of probiotics in functional GI disorders is still low and needs further refinement. In consideration of the presumed beneficial effect of probiotics on joint health (see above), after careful assessment of the GI status—Especially in symptomatic patients -, regular intake of prebiotics and probiotics (e.g., 1–6 billion CFU/day) may be considered in JHS/EDS-HT.

CONCLUSIONS

Previous sections illustrate the potential applications of nutritional supplementations in JHS/EDS-HT. Although all the above listed recommendations are based on low-level evidence data, they may be organized in a holistic schedule of administration in the JHS/EDS-HT patient (Table V). Some dietary supplements are optimal for prevention of osteoarthritis and a few additional features, while others are best suitable for treatment of specific complaints, mostly including pain, fatigue and epithelial/vascular fragility. Listed dosages and recommendations may be used in the practice, but their applications need caution. All reported dosages are extracted from previous experimental works carried out within a discrete time window or from expert reviews. Therefore, all prescriptions should be always personalized considering patient's age and co-morbidities, and their efficacy (and possible side-effects) should be periodically monitored by close follow-ups. Our experience on JHS/EDS-HT envisages the urgent need of more efficacious treatment strategies, which should be planned and tested with a holistic approach. In this perspective, nutritional supplementations, together with other lifestyle interventions, are likely to become a centerpiece of the future prevention and, perhaps, treatment approach to JHS/EDS-HT.

FINAL REMARKS

In this paper, pertinent literature was reviewed in order to stress two issues: (i) GI manifestations are diverse and common in JHS/EDS-HT, and often represent a major contributor to the overall disability of the affected individual; (ii) nutrient deficiencies may participate in the onset or worsening of selected clinical manifestations of JHS/EDS-HT (e.g., pain, fatigue, osteoarthritis, reduced bone mass, and skin and mucosal features), and that tailored nutritional supplementations may improve patients' quality of life. Investigating the link between these two apparently separated concepts could be one of the future aims of clinical research in JHS/EDS-HT. In the first part of this paper, the dyadic nature of GI involvement in JHS/EDS-HT has been emphasized with a wide range of functional and structural manifestations. Both could directly (e.g., altered gut structure) or indirectly (e.g., dysmotility leading to altered microbiota) influence gut permeability to micronutrients. In addition, there is a weak support of an increased rate of bowel inflammatory conditions (i.e., celiac disease, Crohn disease and eosinophilic esophagitis) in gJHM and JHS/EDS-HT. If supported by more robust

TABLE V. Proposed Nutritional Supplementation in Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type

Supplementation	Quantity per dose	No. of doses/day	Note
Prevention			
Eicosapentaenoic and decosahexaenoic acid	3 g	1	Prevention of osteoarthritis and epithelial fragility
Glucosamine/chodroitin/hyaluronan	2 mg(/kg)/1.2 mg/75 mg	1	Prevention of osteoarthritis
Phytoflavonoids/polyphenols	750 mg	2	Prevention of osteoarthritis and epithelial fragility
S-adenosylmethionine	500 mg	1	Prevention of osteoarthritis
Selenium/manganese/boron/zinc	300 μg/10 mg/8 mg/50 mg	1	Prevention of osteoarthritis
Undenatured collagen II	40 mg	1	Prevention of osteoarthritis
Vitamin C	250 mg	2	Prevention of osteoarthritis, and capillary and epithelial fragility
Vitamin D_3	400–800 IU	1	Prevention of osteoarthritis and reduced bone mass
Vitamin E	200 IU	1	Prevention of osteoarthritis and epithelial fragility
Vitamin K_2	1 mg	1	Prevention of osteoarthritis
γ-linolenic acid	1 g	1	Prevention of osteoarthritis
Treatment			
Acetyl-L-carnitin	250 mg	1	Treatment of chronic fatigue; treatment of xerophthalmia
Co-enzyme Q10	100–400 mg	1	Treatment of chronic fatigue
Isotonic liquids	2–2.5 L	—	Treatment of fatigue; treatment of xerophthalmia
Magnesium oxide/gluconate	400 mg/100 mg	1	Treatment of chronic/neurogenic/neuropathic pain
Melatonin	3–5 mg	1 (bedtime)	Sleep regularization
Membrane phospholipids	2,000 mg	1	Treatment of chronic fatigue
NADH	35 mg	1	Treatment of chronic fatigue
Palmitoylethanolamide	300–600 mg	2	Treatment of chronic/neuropathic pain
Probiotics	1–6 billion CFU	1	Treatment of irritable bowel syndrome (optimal pros vs. cons evaluation)
Thiamine/pyridoxine/cyanocobalamin	100 mg/100 mg/5 mg	1	Treatment of chronic/neuropathic pain (i.e., improvement of analgesic effect of painkillers)
Vitamin A	0.8 mg	1	Treatment of dry eye (after careful clinical investigations, and exclusion of pregnancy status and planning)
Vitamin C	500–3,000 mg	1	Treatment of skin/capillary/mucosal fragility
Vitamin D_3	880 IU	1	Treatment of reduced bone mass
α-ketoglucaric acid	180 mg	1	Treatment of chronic fatigue

data in adequately selected samples, the link between gut mucosal integrity and immune dysregulation, and JHS/EDS-HT may open a new era of investigative studies aimed at understanding the pathologic bases of many JHS/EDS-HT-associated complaints and, hopefully, at identifying more specific therapies.

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