Functional Digestive Symptoms and Quality of Life in Patients with Ehlers-Danlos Syndromes: Results of a National Cohort Study on 134 Patients

Jean-David Zeitoun1,2*, Jérémie H. Lefèvre3,4, Vincent de Parades5, César Séjourné6, Iraj Sobhani7, Benoît Coffin8,9, Claude Hamonet10,11

1 Department of Gastroenterology and Nutrition, Saint-Antoine Hospital, APHP, Paris, France, 2 Department of Proctology, Deaconesses Hospital, Paris, France, 3 Department of Digestive and General Surgery, Saint-Antoine Hospital, APHP, Paris, France, 4 University Paris VI, Paris, France, 5 Department of Proctology, Saint-Joseph Hospital, Paris, France, 6 Private Office, Marolles en Hurepoix, France, 7 Department of Gastroenterology, Henri Mondor Hospital, APHP, Créteil, France, 8 Department of Gastroenterology, Louis Mourier Hospital, APHP, Colombes, France, 9 University Denis Diderot-Paris VII, Paris, France, 10 Department of Physical and Rehabilitation Medicine, Hôtel Dieu Hospital, APHP, Paris, France, 11 Department of Medicine, University Paris-East- Créteil (UPEC), France

Abstract

Background and Objectives: Ehlers-Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders. Gastrointestinal manifestations in EDS have been described but their frequency, nature and impact are poorly known. We aimed to assess digestive features in a national cohort of EDS patients.

Methods: A questionnaire has been sent to 212 EDS patients through the French patient support group, all of which had been formally diagnosed according to the Villefranche criteria. The questionnaire included questions about digestive functional symptoms, the GIQLI (Gastrointestinal Quality of Life Index), KESS scoring system and the Rome III criteria.

Results: Overall, 135 patients (64% response rate) completed the questionnaire and 134 were analyzable (123 women; 91%). Mean age and Body Mass Index were respectively 35±14.7 years and 24.3±6.1 kg/m². The most common EDS subtype was hypermobility form (n=108; 80.6%). GIQLI and KESS median values were respectively 63.5 (27-117) and 19 [13.5-22]. Eighty four percent of patients had functional bowel disorders (FBD) according to the Rome III criteria. An irritable bowel syndrome according to the same criteria was observed in 64 patients (48%) and 48 patients (36%) reported functional constipation. A gastro-esophageal reflux disease (GERD) was reported in 90 patients (68.7%), significantly associated with a poorer GIQLI (60.5±16.8 versus 75.9±20.3; p<0.0001). GIQLI was also negatively impacted by the presence of an irritable bowel syndrome or functional constipation (p=0.007). There was a significant correlation between FBD and GERD.

Conclusions: Natural frequency of gastrointestinal manifestations in EDS seems higher than previously assessed. FBD and GERD are very common in our study population, the largest ever published until now. Their impact is herein shown to be important. A systematic clinical assessment of digestive features should be recommended in EDS.

Introduction

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders mainly characterized by joint hypermobility, skin hyperextensibility and tissue fragility [1]. It was described at the beginning of the 20th century by two dermatologists, Edvard Ehlers and Henri-Alexandre Danlos [2,3]. In 1997, the Villefranche classification defined the 6 major forms of EDS [4]. The classical type (I), hypermobility type (II) and vascular type (III) are the most frequent clinical presentations while the 3 remaining forms (kyphoscoliosis type, arthrodysplasia type, dermatosparaxis type) seem to be very rare (see Table 1). Mutations in type V and type III collagen are respectively involved in classical and vascular EDS while the 3 last forms of EDS are biologically related to the processing of
Digestive Symptoms in Ehlers-Danlos Syndromes

Table 1. Nosology from the Villefranche Classification [1].

| Ehlers-Danlos Syndrome | Inheritance | Major diagnostic criteria |
|------------------------|-------------|--------------------------|
| I, classical type      | Autosomal dominant | Skin hyperextensibility |
|                        |             | Widened atrophic scars   |
|                        |             | Joint hypermobility      |
| II, hypermobility type | Autosomal dominant | Skin involvement         |
|                        |             | Generalized joint hypermobility |
| III, vascular type     | Autosomal dominant | Thin, translucent skin   |
|                        |             | Arterial/intestinal/uterine fragility or rupture |
|                        |             | Extensive bruising       |
|                        |             | Characteristic facial appearance |
| IV, kyphoscoliosis type| Autosomal recessive | Generalized joint laxity |
|                        |             | Severe muscle hypotonia at birth |
|                        |             | Scoliosis at birth, progressive |
|                        |             | Scleral fragility and rupture of the ocular globe |
| V, arthrochalasia type | Autosomal dominant | Severe generalized joint hypermobility with recurrent subluxations |
| VI, dermatosparaxis type | Autosomal recessive | Congenital bilateral hip dislocation |
|                        |             | Severe skin fragility    |
|                        |             | Sagging, redundant skin  |

doi: 10.1371/journal.pone.0080321.t001

At least one by a single national expert practitioner in EDS (CH) and all were formally diagnosed as having EDS according to Villefranche criteria [1]. Joint hypermobility was assessed using the Beighton Scale [8]. There was no incentive to complete the questionnaire. Patients who did not complete the survey after one month received a reminder once. It was preplanned that patients who would have responded to the questionnaire improperly would not be recalled. The questionnaire included relevant general and demographic characteristics, and questions about digestive symptoms. Gastro-esophageal reflux disease (GERD) was defined as it is usually done in the scientific literature as the occurrence of either heartburn and (or) regurgitations. Most other esophageal and extraesophageal symptoms of GERD were included in the questionnaire according to their listing in a reference paper [9]. Additionally, 3 internationally validated or at least commonly accepted questionnaires were included which were the following: irritable bowel syndrome (IBS) and functional constipation (FC) were defined according to the Rome III criteria. Severity of constipation was determined by using the Kess score. Impact of these symptoms on quality of life was measured by the Gastrointestinal Quality of Life Index [10] (GIQLI). All these three questionnaires had been translated in French. For the Rome III criteria and the Kess score, we used the French versions of the French Group of Neurogastroenterology (Groupe Français de Neurogastroentérologie, GFNG) which is the official study group of motility and sensitivity, affiliated to the French National Society of Gastroenterology (SNFGE) and the European Society of Neurogastroenterology and Motility (ESNM). For the GIQLI, we used a validated French version of the questionnaire [11]. Both English and French complete versions of the questionnaires can be found in the Appendix. Data were collected in September 2012 by a single person and entered into a dedicated and anonymized database. This study was approved by the French National Commission for Data Protection (Commission Nationale Informatique et Libertés). All patients were fully informed according to the French ethics law and gave written consent.

Statistical analysis

Statistical analysis was performed by using JMP9 (SAS Institute, USA). Data are shown as the prevalence, mean (standard deviation), or median (range). Continuous data were compared by using the Mann-Whitney U test. Comparison of mean values between three groups (IBS, FC, and no IBS or FC) was performed using ANOVA test. All statistical tests were two-sided, with the threshold of significance set at p<0.05.

Results

Out of the 212 patients at baseline, 113 patients returned a questionnaire by e-mail and 22 by mail. Overall, 135 returned a completed questionnaire (64% response rate) among which 134 were analyzable. Demographics and clinical characteristics are shown in Table 2. Gastrointestinal manifestations had been starting before other symptoms of EDS in 54 patients (44.6%) and before EDS formal diagnosis in 96 patients (74.4%).
manifestation of EDS was observed before the age of 18 in 94 patients (69.6%).

Upper GI symptoms: Gastro-esophageal reflux disease (GERD) and dyspepsia

Frequencies of different symptoms of GERD or dyspepsia are shown in Table 3. One hundred and seven patients complained from heartburn and/or regurgitations (79.3%). Seventy-two patients (55%) had undergone upper endoscopy, among which 33 of them (45.8%) were declared to be normal or unremarkable. Nineteen patients had a hiatal hernia on endoscopy.

Table 2. Demographics and clinical characteristics.

| Characteristics               | n (%)    |
|------------------------------|----------|
| Age – mean (± SD)            | 35 (14.7) |
| Female                       | 123 (91) |
| Weight – mean (kg ± SD)      | 66.6 ± 18.9 |
| Height – mean (cm ± SD)      | 164.9 ± 10.2 |
| Body mass index – mean (± SD)| 24.3 ± 6.1 |
| Age at first symptoms of EDS |          |
| Infant (0-2 years)           | 26 (19.3%) |
| Childhood 2-10 years)        | 41 (30.4%) |
| Adolescence (11-17 years)    | 27 (20%) |
| Adult (> 18 years)           | 29 (21.5%) |
| Unknown                      | 12 (8.9%) |
| Tobacco                      | 39 (31.0) |
| Daily work                   | 39 (32.5) |
| Classical type               | 11 (8.2) |
| Hypermobility type           | 108 (80.6) |
| Vascular type                | 3 (2.2) |
| Other – Mixed forms          | 12 (9) |

Table 3. Frequencies of upper GI symptoms: gastro-esophageal reflux disease (GERD) or dyspepsia.

| Symptoms                                  | n (%)   |
|-------------------------------------------|---------|
| Heartburn                                 | 90 (68.7) |
| Regurgitations                            | 90 (68.7) |
| Symptoms worsened by decubitus            | 82 (62.6) |
| Chronic cough                             | 47 (36.2) |
| Laryngitis                                | 75 (56.8) |
| Erosion of dental enamel                  | 67 (51.5) |
| Asthma                                    | 58 (45) |
| Dysphagia                                 | 82 (62.6) |
| Epigastric pain                           | 104 (78.8) |
| Nausea                                    | 92 (70.8) |
| Postprandial fullness                     | 88 (67.2) |
| Belching                                  | 91 (70.5) |

GIQLI was also significantly lower in case of IBS or FC compared to no FBD (p=0.0007) (Figure 4).

Discussion

In the present survey, we have shown that the frequency of functional gastrointestinal manifestations in EDS was highly prevalent, much higher than previously assessed. IBS, functional constipation and GERD were present in respectively 48%, 36% and 79% of our study population, the largest ever published until now. Their impact is herein shown to be important.

Ehlers-Danlos syndromes (EDS) are a genetically and clinically heterogeneous group of disorders characterized by fragility of the soft connective tissues [12]. The Villefranche classification recognizes six EDS subtypes among which classical, hypermobility and vascular types are the most frequent ones [1]. Most publications concerning gut symptoms in patients with EDS are dealing with vascular type, certainly because it is the most serious one, but gut symptoms occurring in classical or hypermobility types, which affect the majority of patients are paradoxically less documented. No standardized approach has ever been adopted to describe them properly. Only life-threatening complications such as spontaneous perforation or massive bleeding have been reported but one might question the representativeness of such reports regarding the whole population of EDS since it was generally in vascular types of EDS. Our survey is, to our knowledge, the largest in an EDS national cohort assessing gastrointestinal profile of affected patients. All subjects have been formally diagnosed after clinical examination by a single national expert, (CH) according to the validated international Villefranche classification.

Lower GI symptoms: irritable bowel syndrome and functional constipation

Sixty-four patients (48%) reported irritable bowel syndrome (IBS) according to the Rome III criteria (Table 4) with a homogenous repartition according to stool consistency. Forty-eight patients (36%) displayed functional constipation (FC) according to the Rome III criteria. KESS median score was 19 [13.5-22] and 117 patients (87.3%) had a KESS score > 9, which is the generally accepted cut-off for constipation. Patients with functional constipation had a significant worse KESS score (21.5±0.82 vs. 15.8±0.84; p<0.0001). There was a statistically significant association between FBD and GERD: 89.2% (91/102) patients with FBD also had GERD whereas 59.1% (13/22) of patients without FBD were displaying GERD symptoms (p=0.002) (Figure 1).

Impact on quality of life

Median GIQLI was 63.5 [27-117]. The mean score was significantly lower when compared with a French control population of 238 individuals [11] (65.3±1.65 vs. 128.0±0.81; p<0.0001; see Figure 2). Details and subscales results are presented in Table 5. All subscales scores were significantly lower for patients with EDS when compared to the control groups (p<0.0001), see Figure 3. GERD was significantly associated with a worst GIQLI (60.5 ± 16.8 versus 75.9 ± 20.3; p<0.0001). GIQLI was also significantly lower in case of IBS or FC compared to no FBD (p=0.0007) (Figure 4).
### Table 4. Rome III criteria for Irritable Bowel Syndrome (IBS) and Functional Constipation in the Ehlers-Danlos Syndromes cohort.

| Symptoms                                                                 | N (%) | Diagnosis                                      |
|-------------------------------------------------------------------------|-------|------------------------------------------------|
| Recurrent abdominal pain or discomfort at least 3 days per month in the last three months associated with: |  | 64 patients having IBS according to the Rome III criteria |
| Improvement with defecation                                             | 78    |                                                |
| Onset associated with a change in frequency of stool                    | 55    |                                                |
| Onset associated with a change in form (appearance) of stool            | 66    |                                                |
| Irritable Bowel Syndrome (IBS) diagnosis                                |  |                                                |
| 3 associated above features                                             | 41    |                                                |
| 2 associated above features                                             | 23    |                                                |
| 1 above feature                                                         | 38    |                                                |
| IBS with constipation                                                    | 18 (28%) |                                                |
| IBS with diarrhea                                                       | 18 (28%) |                                                |
| IBS mixed                                                               | 19 (30%) |                                                |
| Unsubtyped IBS                                                          | 9 (14%) |                                                |
| Diagnostic criteria for functional constipation                         |  |                                                |
| Fewer than 3 defecations per week                                       | 37    |                                                |
| Lumpy or hard stools in at least 25% of defecations                      | 64    |                                                |
| Straining during at least 25% of defecations                            | 93    |                                                |
| Sensation of incomplete evacuation for at least 25% of defecations      | 98    |                                                |
| Sensation of anorectal obstruction/blockage for at least 25% of defecations | 54    |                                                |
| Manual maneuvers to facilitate at least 25% of defecations              | 29    |                                                |
| Functional Constipation Diagnosis                                       |  | 48 patients having functional constipation according to the Rome III criteria |
| 6 associated above features                                             | 5     |                                                |
| 5 associated above features                                             | 8     |                                                |
| 4 associated above features                                             | 6     |                                                |
| 3 associated above features                                             | 16    |                                                |
| 2 associated above features                                             | 13    |                                                |

doi: 10.1371/journal.pone.0080321.t004

![Flow Chart](https://example.com/flowchart.png)

**Figure 1. Flow Chart of the functional bowel disorders among the population of Ehlers-Danlos syndrome.**

doi: 10.1371/journal.pone.0080321.g001
criteria. Thus, diagnosis of EDS in the respondents of our survey is thought to be reliable and other phenotypically related conditions must have been excluded. Another strength of our study is the use of internationally validated questionnaire and scoring systems to assess clinical features of recruited patients. The major findings of the current study are that gastrointestinal manifestations are very common and generally not specific, frequently important and that they can have a strong impact on quality of life. Eighty four percent of the studied population had FBD among which 57% had IBS and 43% functional constipation. Approximately 80% of patients had GERD. There was a statistically significant association between upper and lower GI symptoms. Overall, median GIQLI was 63.5 [51.8-76.8], which is extremely low compared to most publications and it is of note that GERD and lower GI symptoms negatively influenced this scoring system. All these findings clearly indicate that digestive manifestations in EDS are of major relevance and may have been previously underdiagnosed and undertreated. All reported symptoms are remarkably nonspecific and this could partly explain why little attention has been paid until now to these clinical manifestations. In addition, no severe complication has been described in our population, emphasizing the clear distinction between rare but serious complications of EDS vascular type and other common benign but disabling manifestations, for which literature is scarce. Many questions remain unanswered, among which the pathophysiology of reported symptoms. One might hypothesize that tissue hyperextensibility of the gastrointestinal tract could play a role but proprioceptive disorders as well as dysautonomic syndrome which are very common in EDS [13] could also contribute to gastrointestinal manifestations. In addition, the marked preponderance of affected women vs. men in EDS and especially hypermobile type, although previously documented, is still an unexplained feature [6]. Also, current treatment for gastrointestinal symptoms is empirical, often unsatisfactory (data not shown) and further research is needed. At least, a systematic assessment of gastrointestinal symptoms should be recommended in EDS patients in order not to miss a major source of complaints in this population. Whether endoscopic examinations are necessary and at high risk of complication, in particular perforation, is an unresolved question. In our experience, upper gastrointestinal endoscopy seems safe and useful to detect Barrett’s esophagus in this population with a high rate of GERD. On the other hand, the matter of colonoscopy is more sensitive. Indeed, the risk of perforation is clearly significant in vascular EDS and colonoscopy should be strongly discouraged in this population. Additionally, the risk of any complication (perforation or bleeding) is theoretically increased in other EDS subtypes, although not quantifiable and although no patient in our cohort underwent any complication. CT colonography could be an alternative option to rule out polyps or tumor but one should keep in mind the risk of repeated irradiating exams in this population with frequent orthopedic complications.

Our study has several limitations. The first one is the absence of control group (except regarding GIQLI for which we used a historical control French population) which precludes definitive conclusions from this survey. However, there is an abundant literature about FBD and GERD and comparisons with reported natural frequencies and severity in historical populations allow us to assume that gastrointestinal manifestations in EDS are particularly common and linked to the condition. For instance, a French survey conducted on a

Figure 2. GIQLI score (individual spot and means) according to the presence of Ehlers-Danlos syndrome.

doi: 10.1371/journal.pone.0080321.g002
nationally representative sample reported a prevalence of IBS (according to the Rome II criteria which were slightly different from the Rome III criteria) to be lower than 5% [14]. Another epidemiologic mail survey found that prevalence of GERD reached 8% in another sample of 8000 subjects representative of the French adult population [15]. In addition, we cannot rule out the possibility of response bias, although our percentage of returned questionnaires was slightly higher than the generally required 60% response rate [16]. Although many patients of the questioned cohort had genetic testing, we were not allowed to collect these data in the present study, which is another potential deficiency. However, most of our population was affected by hypermobility type, consistently with literature and the genetic basis of this EDS form is lacking. At last, we cannot establish how many patients with differential diagnosis (such as

Table 5. Details of GIQLI score and subscales.

| Items                                      | Mean±SD       | Subscale score | Theoretical Range | Mean ± SD | Median (min-max) |
|--------------------------------------------|---------------|----------------|-------------------|-----------|------------------|
| **Physical Well-Being**                    |               |                |                   |           |                  |
| Item 8 (Pleasure and appetite)             | 1.60±1.18     |                |                   |           |                  |
| Item 15 (Fatigue)                          | 0.46±0.71     |                |                   |           |                  |
| Item 16 (Feeling unwell)                   | 1.13±0.92     |                |                   |           |                  |
| Item 18 (Appearance)                       | 1.62±1.47     |                |                   |           |                  |
| Item 19 (Physical strength)                | 0.82±1.13     |                |                   |           |                  |
| Item 20 (Endurance)                        | 0.35±0.77     |                |                   |           |                  |
| Item 21 (Feeling unfit)                    | 0.40±0.78     |                |                   |           |                  |
| Item 22 (Daily activities)                 | 1.94±1.12     |                |                   |           |                  |
| Item 23 (Leisure activities)               | 1.44±1.12     |                |                   |           |                  |
| Item 33 (Nausea)                           | 2.08±1.22     |                |                   |           |                  |
| **Gastrointestinal digestion**             |               |                |                   |           |                  |
| Item 1 (Pain in abdomen)                   | 1.65±0.97     |                |                   |           |                  |
| Item 2 (Fullness in abdomen)               | 1.63±1.27     |                |                   |           |                  |
| Item 3 (Bloating)                          | 1.47±1.17     |                |                   |           |                  |
| Item 4 (Flatus)                            | 1.89±1.28     |                |                   |           |                  |
| Item 5 (Burping/belching)                  | 1.94±1.24     |                |                   |           |                  |
| Item 6 (Abdominal noises)                  | 1.73±1.18     |                |                   |           |                  |
| Item 27 (Regurgitation)                    | 2.01±1.22     |                |                   |           |                  |
| Item 28 (Eating speed)                     | 2.06±1.38     |                |                   |           |                  |
| Item 32 (Constipation)                     | 1.55±1.32     |                |                   |           |                  |
| Item 35 (Heartburn)                        | 2.09±1.28     |                |                   |           |                  |
| **Gastrointestinal defecation**            |               |                |                   |           |                  |
| Item 7 (Bowel frequency)                   | 2.56±1.26     |                |                   |           |                  |
| Item 26 (Impaired sexual life)             | 1.55±1.26     |                |                   |           |                  |
| Item 30 (Bowel Urgency)                    | 2.44±1.18     |                |                   |           |                  |
| Item 31 (Diarrhoea)                        | 2.82±1.12     |                |                   |           |                  |
| Item 34 (Blood in stool)                   | 3.45±0.94     |                |                   |           |                  |
| Item 36 (uncontrolled stools)              | 3.47±0.91     |                |                   |           |                  |
| **Mental Well Being Scale**                |               |                |                   |           |                  |
| Item 10 (Coping with stress)               | 1.90±1.02     |                |                   |           |                  |
| Item 11 (Sad about illness)                | 2.02±1.07     |                |                   |           |                  |
| Item 12 (Nervous about illness)            | 2.13±1.20     |                |                   |           |                  |
| Item 13 (Happy with life)                  | 2.23±0.96     |                |                   |           |                  |
| Item 14 (Frustrated by illness)            | 1.56±0.92     |                |                   |           |                  |
| **Items not included in a subscale**       |               |                |                   |           |                  |
| Item 9 (Restricted eating)                 | 2.10±1.38     |                |                   |           |                  |
| Item 17 (Wake up at night)                 | 0.89±1.27     |                |                   |           |                  |
| Item 24 (Bothered by treatments)           | 2.64±1.19     |                |                   |           |                  |
| Item 25 (Worsened relations)               | 1.60±1.26     |                |                   |           |                  |
| Item 29 (Dysphagia)                        | 2.61±1.19     |                |                   |           |                  |
| **Overall score**                          |               |                |                   |           |                  |
| **Subscale score**                         |               |                |                   |           |                  |

SD = Standard Deviation; GIQLI = Gastrointestinal Quality of Life Index.
doi: 10.1371/journal.pone.0080321.t005

Digestive Symptoms in Ehlers-Danlos Syndromes

PLOS ONE | www.plosone.org 6 November 2013 | Volume 8 | Issue 11 | e80321
neuromuscular disorders or other connective tissue disorders) were excluded from the present cohort.

In summary, our study is to date the largest conducted survey specifically assessing the natural frequency, nature and impact of functional gastrointestinal manifestations in EDS. It emerges that digestive manifestations are extremely common, most frequently nonspecific and not serious but with major consequences on quality of life. A systematic clinical assessment should be recommended in EDS population and further studies are needed to elucidate the pathophysiology of these disorders and to improve therapeutic management.

Supporting Information

Appendix S1. Questionnaire. (DOCX)

Figure 3. Subscales of the GIQLI between patients with EDS (box with white lines) and control population (filled box) and results of the Student comparison.
doi: 10.1371/journal.pone.0080321.g003

Figure 4. GIQLI score according to the presence and the type of functional bowel disorders (FC: functional constipation; IBS: irritable bowel syndrome).
doi: 10.1371/journal.pone.0080321.g004

Acknowledgements

All authors are grateful to patients who responded to the submitted questionnaire and would like to thank the French patient support group for their help in collecting data. JD Zeitoun would like to thank Pr Hervé Maisonneuve for his precious advice and Pr Karem Slim for his gracious help by giving the data of his pivotal study.

Author Contributions

Contributed to the conception of the study: JDZ JHL VdP CS IS BC CH. Contributed to the acquisition of data and their interpretation: JDZ JHL VdP CS IS BC CH. Contributed to the final draft of the article or to its critical revision: JDZ JHL VdP CS IS BC CH. Approved the final version: JDZ JHL VdP CS IS BC CH. Proceeded to clinical examination for all included patients: CH. Performed the main part of the statistical analysis: JHL.
References

1. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ (1998) Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet 77: 31-37.

2. Danlos M (1908) Un cas de cutis laxa avec tumeurs par contusion chronique des coudes et des genoux (xanthome juvénile pseudo-diabétoque de MM Hallopeau et Marc de Lépinay). Bull Soc Franc Derm Syph 19: 70-72.

3. Ehlers E (1901) Cutis laxa, neigung zu haemorrhagien in der haut, lockerung mehrerer artikulationen. Derm Zschr 18: 173-175.

4. De Paepe A, Malfait F (2012) The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genet 82: 1-11. doi:10.1111/j.1399-0004.2012.01858.x. PubMed: 22353005.

5. Pepin M, Schwarze U, Superti-Furga A, Byers PH (2000) Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 342: 673-680. doi:10.1056/NEJM200003093421001. PubMed: 10706896.

6. Castori M, Camerota F, Celletti C, Danese C, Santilli V et al. (2010) Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: a pilot study on 21 patients. Am J Med Genet A 152A: 556-564. doi:10.1002/ajmg.a.33231. PubMed: 20140961.

7. Beighton PH, Murdoch JL, Votteler T (1969) Gastrointestinal complications of the Ehlers-Danlos syndrome. Gut 10: 1004-1008. doi:10.1136/gut.10.12.1004. PubMed: 5308459.

8. Beighton P, Solomon L, Soskolne CL (1973) Articular mobility in an African population. Ann Rheum Dis 32: 413-418. doi:10.1136/ard.32.5.413. PubMed: 4751776.

9. Kahrlas PJ (2008) Clinical practice. Gastroesophageal reflux disease. N Engl J Med 359: 1700-1707. doi:10.1056/NEJMcp0804684. PubMed: 18923172.

10. Eypasch E, Williams JL, Wood-Dauphiné S, Ure BM, Schmülling C et al. (1995) Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg 82: 216-222. doi: 10.1002/bjs.1800820229. PubMed: 7749697.

11. Slim K, Bousquet J, Kwiatkowski F, Lescure G, Pezet D et al. (1999) First validation of the French version of the Gastrointestinal Quality of Life Index (GIQLI). Gastroenterol Clin Biol 23: 25-31. PubMed: 10219601.

12. Callewaert B, Malfait F, Loeys B, De Paepe A (2008) Ehlers-Danlos syndromes and Marfan syndrome. Best Pract Res Clin Rheumatol 22: 165-189. doi:10.1016/j.berh.2007.12.005. PubMed: 18338988.

13. Castori M, Morlino S, Celletti C, Celli M, Morrone A et al. (2012) Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type); principles and proposal for a multidisciplinary approach. Am J Med Genet A 155A: 2055-2070. doi:10.1002/ajmg.a.35483. PubMed: 22786715.

14. Dapoigny M, Bellanger J, Bonaz B, Bruley des Varannes S, Bueno L et al. (2004) Irritable bowel syndrome in France: a common, debilitating and costly disorder. Eur J Gastroenterol Hepatol 16: 995-1001. doi: 10.1097/00042737-200410000-00008. PubMed: 15371923.

15. Bretagne JF, Richard-Molard B, Honnorat C, Caekaert A, Barthelemy P (2006) Gastroesophageal reflux in the French general population: national survey of 8000 adults. Presse Med 35: 23-31. doi:10.1016/S0755-4982(06)74515-8. PubMed: 16462660.

16. Johnson TP, Wislar JS (2012) Response rates and nonresponse errors in surveys. JAMA 307: 1805-1806. doi:10.1001/jama.2012.3532. PubMed: 22650194.