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Prevalence of joint hypermobility, hypermobility spectrum disorder and hypermobile Ehlers-Danlos syndrome in a university population: an observational study

Filiz Tuna

Department of Physical Therapy and Rehabilitation, Trakya University Faculty of Health Science, Edirne, Turkey

ABSTRACT

Objectives: To investigate the prevalence of joint hypermobility classes, hypermobility spectrum disorders, hypermobile Ehlers-Danlos syndrome and their relations with sex ina university population. They are notable topics in rehabilitation, since they represents the basis for some secondary disability conditions.

Methods: Three hundred and thirty-five students met the inclusion criteria (university students who are not disabled, without known disease, aged 18-25 years). Joint hypermobility were classified as generalized, peripheral and localized asymptomatic or hypermobility spectrum disorders. Hypermobile Ehlers-Danlos syndrome was defined according to; 1) Brighton criteria with cut-off Beighton scoring ≥ 4/9, 2) Villefranche criteria with cut-off Beighton scoring ≥ 5/9, and 3) The 2017 International Classification of Ehlers-Danlos syndrome.

Results: In total, 77.3% (n = 259) of participants had any class of joint hypermobility and 25.9% (n = 87) of them had generalized class. Asymptomatic joint hypermobility and hypermobility spectrum disorders prevalence in a university population were found to be 38.8% and 38.5%, respectively. Generalized, peripheral, localized asymptomatic joint hypermobility and hypermobility spectrum disorders were found; 13.1%, 4.2%, 21.5%, and 12.8%, 7.5%, 18.2%, respectively. Prevalence of hypermobile Ehlers-Danlos syndrome according to three classifications were found to be; 19.4%, 15.2%, and 1.2%, respectively.

Conclusions: The most common classes are localized asymptomatic joint hypermobility in women and localized hypermobility spectrum disorders in men. Awareness of the prevalence of joint hypermobility, hypermobility spectrum disorders and hypermobile Ehlers-Danlos syndrome in healthy young population may contribute prevention of disability.

Keywords: Joint laxity, musculoskeletal complications, chronic pain, myopia, dental braces, soft tissue problems

Joint hypermobility is a condition in which a joint has a range of motion greater than normal [1]. Joint hypermobility, hypermobility spectrum disorders, and hypermobile Ehlers-Danlos syndrome (EDS) are notable topics in rehabilitation, since they represents the basis for some secondary disability condi-

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Address for correspondence: *Filiz Tuna., Trakya University School of Health Science, , Department of Physical Therapy and Rehabilitation, 22030, Edirne, Turkey. E-mail: drftuna@hotmail.com, Tel: +90 284 2133042*

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tions [2, 3]. The 2017 International Classification has been published for update the EDS nosology and develop best practice clinical guidelines on diagnosis of EDS recently [4]. Although hypermobile EDS is defined as benign, it is a structural predisposition leading to a decline in the quality of life due to multi-systemic manifestations [5-9].

Shepert *et al*. [10] published their longitudinal cohort study describing the natural history and the prognosis in 101 children with joint hypermobility syndrome or hypermobility-type EDS according to the Brighton and Villefranche criteria. Pain, fatigue, and psychological distress had a significant impact on disability that affect patients with generalized joint hypermobility, joint hypermobility syndrome or hypermobility-type EDS considerably [3, 10, 11]. They reported functional impairment as predictive for decreased quality of life over time.Awareness of the prevalence of joint hypermobility, hypermobility spectrum disorders and hypermobile EDS in healthy young university population may contribute recognition, management and prevention of disability. It is important to investigate the situation in university students, because they form a young and dynamic group in terms of future labor force.

Prevalence of generalized joint hypermobility varying from 2% to 57% in different populations [12, 13]. In Turkey, studies report it in healthy subjects between 12.4 and 22 % for women and 6.1-7.7 % for men of varying ages [14-17]. Reasons of variations are different ages or Beighton scoring cut-offs, and lack of consistency in clinical assessment methods. In addition, there is no information about prevalence of localized, peripheral classes of joint hypermobility, hypermobility spectrum disorders and hypermobile EDS according to the old and new criteria.

Our purposes in this research in a university population are; (i) to investigate the prevalenceof new defined classes of asymptomatic joint hypermobility (generalized, peripheral and localizedclasses) and hypermobility spectrum disorders, (ii) to investigate the prevalence of hypermobile EDS, defined according to Brighton, Villefranche and the 2017 International Classification criteria in order to allow comparison with previous studies, and (iii) to investigate relationship between the Beighton scoring, the Brighton criterion and sex.

METHODS

Participants

We conducted an observational (a cross-sectional) study between 2016 and 2017. Trakya University students aged 18-25 years were invited to participate. Our Physical Therapy and Rehabilitation Department is an integrated department of faculty that provides education for a population of 346 residents of Turkey.

A total of 346 students (all of Physical Therapy and Rehabilitation students in Trakya University Faculty of Health Sciences) were targeted. Students voluntarily agreed to participate in the study and informed consent was obtained from each student. Inclusion criteria were; university students who are not disabled, without known disease, and aged 18-25 years. Exclusion criteria were; students with known disease, inappropriate age, and unwilling to participate). Eleven (3.1%) students were not eligible to inclusion criteria (4 students with known disease, 3 students with inappropriate age and 4 students declined to participate). The local ethics committee approved the conduction of the research (BAEK 2016/255).

Procedures

Demographic data of participants, including age, height, and weight, were recorded. Beighton scoring was performed face-to-face with each participant by the same physiatrist [18, 19]. Asymptomatic and symptomatic joint hypermobility (generalized, peripheral, and, localized), were classified according to Beighton scoring, anatomic location of hypermobile joints and accompanying musculoskeletal problems [20]. hypermobile EDS was diagnosed according to three classifications; 1) Brighton criteria with cut-off Beighton scoring $\geq$ 4/9 for generalized joint hypermobility [19], 2) Villefranche criteria with cut-off Beighton scoring $\geq$ 5/9 for generalized joint hypermobility [21], and 3) The 2017 International Classification of EDS [4].

Beighton Scoring

For the Beighton scoring, the following items were evaluated; 1) Placement of hands flat on the floor without bending the knees, 2) Hyperextension of the elbow to $\geq$ 10°, 3) Hyperextension of the knee to $\geq$ 10°, 4) Opposition of the thumb to the volar aspect of

the ipsilateral forearm, and 5) Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90° [18]. The first item for Beighton scoring was calculated as one point; the other items as one points for right and left side. The results were summarized arithmetically, with one score given for each positive item. Joint hypermobility was classified as generalized, peripheral, and localized according to defined Beighton score and anatomic localization of affected joint [20]. Participants with hypermobility in only only hands and/ or feet without involvement of large and axial joints were clasified as peripheral joint hypermobility. Involvement of one or fewer than five joints were defined as localized joint hypermobility [20]. Generalized joint hypermobility was defined in participants firstly as a Beighton scoring of ≥ 4/9 (for Brighton criteria) and secondly with Beighton scoring ≥ 5/9 (for Villefranche and the 2017 International Classification) [19, 21]. Brighton criteria [21] and hypermobile EDS criteria described in the 2017 International Classification [4] were asked, and recorded.

Brighton Criteria

The presence of one of the following criteria was deemed sufficient for hypermobile EDS diagnosis [19]: 1) the presence of any of the four major criteria, 2) one major criterion + two minor criteria, 3) four minor criteria, and 4) two minor criteria [19]. As major criteria, a Beighton scoring of ≥ 4/9 and arthralgia existing over 3 months in four joints were interrogated.In addition, minor criteria (having a Beighton scoring of 1-3/9, arthralgia in 1-3 joint, ossicular dislocations, soft tissue problems with ≥ 3 lesions (e.g., epicondylitis, tenosynovitis, and bursitis), Marfan-like appearance, striae of skin, eyelid laxity and hernia, prolapse, and varicose vein history) were questioned [18, 19]. Positivity of the one of following evaluations were enough for decision of Marfanoid habitus; arm span/height ratio > 1.05,

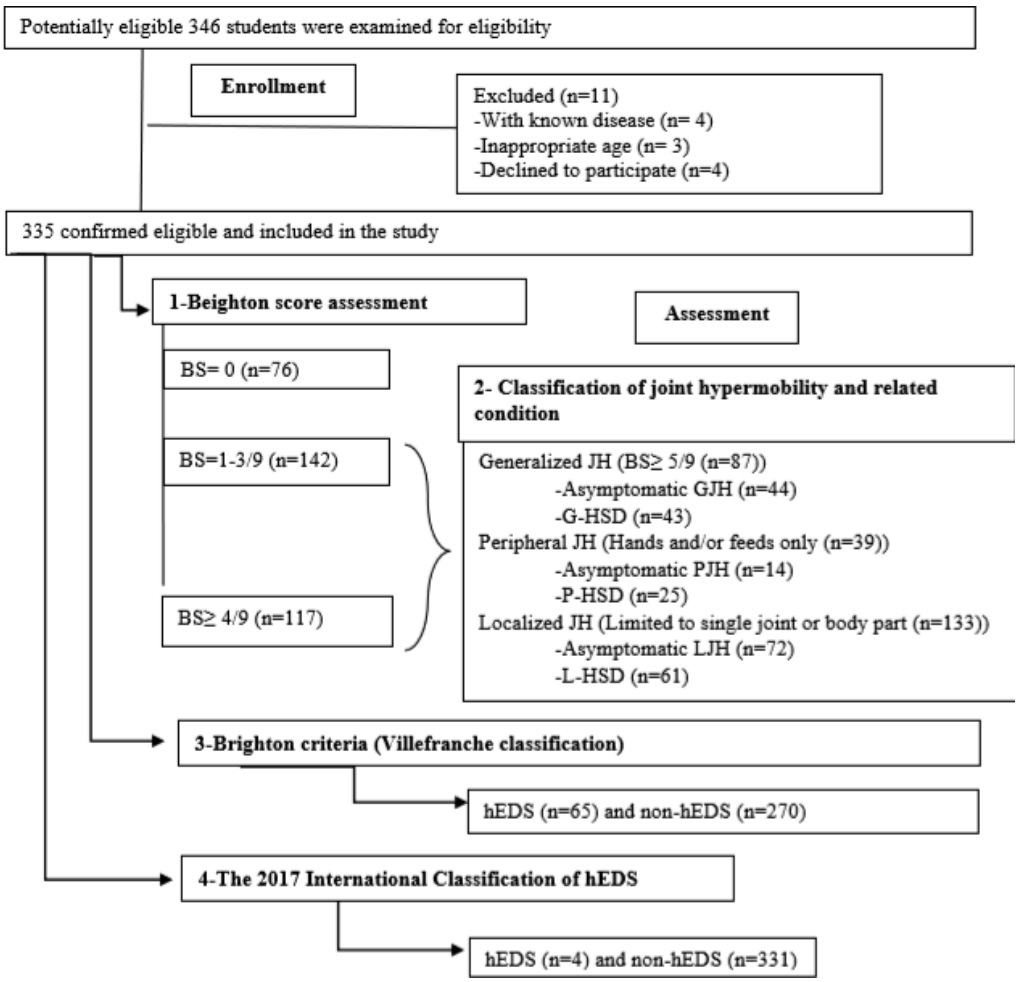

Fig. 1. Flow diagram of study

positive Steinberg sign, and the positive wrist sign and aracnodactilia (bilateral positivity of Steinberg or wrist sign) [4, 18].

Hypermobile EDS Diagnosis According to the 2017 International Classification

A diagnosis of hypermobile EDS was assigned when criteria 1, 2 and 3 simultaneously existed in each participant; (i) Criterion 1 were generalized joint hypermobility with cut-off pointBeighton scoring ≥ 5/9; (ii) Criterion 2 were accepted when at least two of features A, B and C were present in participants. However, feature B, (positive family history of hypermobile EDS) was accepted enough for the diagnosis. Features A was accepted when at least 5 meets of a 12 systemic features of a connective tissue as soft, mild hyperextensibile skin, stria without a history of a significant gain or loss of weight, bilateral piezogenc papules of heel, atrophic scarring, abdominal hernia, genitourinary prolapse, dental crowding, arachnodactyly, prolonged arm span, mild mitral valve prolapse, aortic root dilatation were present in participants [4]. At least one existence of following three musculoskeletal complications were accepted as Feature C; 1) musculoskeletal pain with daily recurrence in at least two limbs, 2) chronic widespread pain. These complications must be present at least for 3 months. 3) At least 3 non-traumatic dislocations in the same joint or more in 2 different joints happening at different times or non-traumatic joint instability at least 2 sites with medical confirmation. (iii) Criterion 3 were accepted when all of following conditions were met;1)Lack of extraordinary skin fragility, 2) Exclusion of further connective tissue disorders, and 3) Exclusion of another diseases with joint hypermobility [4].

Table 1. Participant's demographics and prevalences of joint hypermobility classes, hypermobility spectrum disorders, and hypermobile Ehlers-Danlos syndrome.

	Female Mean (SD)	Male Mean (SD)	Total Mean (SD)				
Age	20.2 (1.6)	21.2 (1.8)	20.5 (1.7)				
Body mass index	20.9 (2.4)	22.6 (2.3)	21.5 (2.5)				
Beighton score (median)	3.0	2.0	2.0				
Classes	n (%)	n (%)	n (%)	OR	95% CI	LR	LR *p* value
Asymptomatic Joint Hypermobility							
Generalized	40 (18.1)	4 (3.5)	44 (13.1)	0.165	0.057-0.472	16.906	**< 0.001**
Peripheral	5 (2.3)	9 (7.9)	14 (4.2)	3.703	1.211-11.324	5.564	**0.018**
Localized	48 (21.7)	24 (21.1)	72 (21.5)	0.961	0.553-1.670	0.020	0.888
Hypermobility spectrum disorder							
Generalized	33 (14.9)	10 (8.8)	43 (12.8)	0.548	0.260-1.156	2.696	0.101
Peripheral	19 (8.6)	6 (5.3)	25 (7.5)	0.591	0.229-1.523	1.278	0.258
Localized	33 (14.9)	28 (24.6)	61 (18.2)	1.855	1.055-3.262	4.528	0.033*
Beighton score of 0/9							
	43 (19.4)	33 (29.0)	76 (22.6)	0.593	0.351-1.002	3.766	0.052

OR odds ratio with 95% confidence interval (CI), LR likelihood ratio and *p* value for the LR

Table 2. Prevalence of the generalized joint hypermobilityand hypermobile Ehlers-Danlos syndrome according to different criteria

	Female N (%)	Male N (%)	Total N (%)	OR	95% CI	LR	LR *p* value
Beighton scorring							
≥ 4/9	92 (41.6)	25 (21.9)	117 (34.9)	0.394	0.235-0.661	13.400	**< 0.001**
≥ 5/9	73 (33.0)	14 (12.3)	87 (25.9)	0.284	0.152-0.531	18.407	**< 0.001**
Jointhypermobilitysyndrome According to Brighton criteria with cut-off Beighton score ≥ 4/9							
	53 (24.0)	12 (10.5)	65 (19.4)	2.687	1.368-5.257	9.443	**0.002**
Hypermobile Ehlers-Danlos syndrome According to Villefranche criteria with cut-off Beighton score ≥ 5/9							
	42 (19.0)	9 (7.9)	51 (15.2)	0.365	0.171-0.780	7.893	**0.005**
Hypermobile Ehlers-Danlos syndrome According to the 2017 International Classification							
	4 (1.8)	0 (0.0)	4 (1.2)	1.525	1.411-1.649	3.353	0.067

OR odds ratio with 95% confidence interval (CI), LR likelihood ratio and *p* value for the LR

Furthermore, participants were questioned for history of the use of dental braces. When accompanying symptoms not meets hypermobile EDS criteria, the joint hypermobility was defined as component of hypermobility spectrum disorder [20]. All the examinations and measurements were performed by the same physiatrist (the author).

Statistical Analysis

Statistical significance is defined by p value of < 0.05. The data of the study were evaluated by IBM SPSS version 20.0 statistical software (Released 2011. IBM Corp., Armonk, NY, USA). Normal distribution of data was examined using Kolmogorov-Smirnov tests. Frequencies and percentages were used for categorical data as descriptive statistics. Median (min-max) values and arithmetic means with standard deviations were used for quantitative data. To evaluate the relationship between sex and Beighton scoring, the participants were divided into groups according to their scores: 0 score, 1-3 score, and ≥ 4 score. The distribution of these groups by sex was then examined. The Pearson chi-square test was used in the analysis of qualitative data. The association between age and Beighton scoring was examined using the Spearman correlation analysis. Likelihoodratios were computed for prevalence of joint hypermobility classes, hypermobility spectrum disorders, hypermobile Ehlers-Danlos syndrome, and Beighton score, with Chi-Square tests.

RESULTS

In total, 335 university students with age between 18 and 25 years, of whom 221 were female and 114 were male, were analyzed in the study (Fig. 1). Demographic data of participants and prevalences in a university population of joint hypermobility classes, hypermobility spectrum disorders, and hypermobile Ehlers-Danlos syndrome were showed in Table 1. In total, 77.3% (n = 259) of participants had any class of joint hypermobility and 25.9% (n = 87) of them had generalized joint hypermobility. Hypermobility spectrum disorders and asymptomatic joint hypermobility were found 38.5% (n = 129) and 38.8% (n = 130), respectively. We found negative correlation between age and Beighton scoring (Spearman's rho; r: -0.332, $p < 0.001$).

The most common classes of joint hypermobility are localized asymptomatic (mainly in women) and localized hypermobility spectrum disorders (mainly in

Table 3. The relationship between sex and Brighton criteria

Female n (%)	Male n (%)	Total n (%)	OR	95% CI	LR	LR *p* value
Major and minor criteria of Brighton						
Arthralgia for longer than 3 months in 4 or more joints						
10 (4.5)	8 (7.0)	18 (5.4)	1.592	0.611-4.153	0.885	0.347
Arthralgia ≥ 3 months in 1-3 joints or back pain ≥ 3 months						
30 (13.6)	9 (7.9)	39 (11.6)	0.546	0.250-1.193	2.498	0.114
Dislocation/subluxation in ≥1 joint or in 1 joint ≥ occasion						
35 (15.8)	21 (18.4)	56 (16.7)	1.200	0.662-2.177	0.356	0.551
Soft tissue problems ≥ 3 lesions						
57 (25.8)	45 (39.5)	102 (30.4)	1.876	1.159-3.037	6.518	**0.011**
Marfanoid habitus						
12 (5.4)	15 (13.2)	27 (8.1)	2.639	1.191-5.849	5.718	**0.017**
Stria, papyraceous scarring						
145 (65.6)	32 (28.1)	177 (52.8)	0.205	0.125-0.335	43.523	**< 0.001**
Drooping eyelids, antimongoloid slanting eyes, or myopia						
93 (42.1)	43 (37.7)	136 (40.6)	0.834	0.524-1.325	0.596	0.440
Varicose veins, hernia, or uterine/rectal prolapse						
8 (3.6)	5 (4.4)	13 (3.9)	1.221	0.390-3.822	0.116	0.733
Total						
221 (100.0)	114 (100.0)	335 (100.0)				

OR odds ratio with 95% confidence interval (CI), LR likelihood ratio and *p* value for the LR

men) (Table 1). Nearly half of joint hypermobility participants have hypermobility spectrum disorders. Generalized joint hypermobility and hypermobile EDS were significantly higher in females (Table 2). Given the Beighton scoring and sex relation, the highest prevalence distributions were 41.6% (n = 92) with ≥ 4 points in females and 49.1% with 1-3 points in males (Pearson χ^2 = 13.191, p = 0.001). The prevalence of skin striae was significantly higher in females, while soft tissue problems and Marfanoid habitus was significantly higher among male participants ($p < 0.05$) (Table 3). The relationship between sex and the questioned 2017 International Classification Criteria is shown in Table 4.

When participants were asked about dental braces statistically significant difference was found between generalized joint hypermobility or hypermobile EDS and participants with a Beighton scoring of 0/9. The prevalences of participants with dental braces in the hypermobile EDS and non-hypermobile EDS groups were 44% (n = 22) and 35.7% (n = 94), respectively (Pearson χ^2; p = 0.268).

Table 4. The relationship between sex and the 2017 International Clasification Criteria

	Female n (%)	Male n (%)	Total n (%)	OR	95% CI	LR	LR *p* value
Criterion 1	73 (33.0)	14 (12.3)	87 (25.9)	3.523	1.885-6.586	18.407	**< 0.001**
Criterion 2	5 (2.3)	1 (0.9)	6 (1.8)	2.616	0.302-22.660	0.923	0.337
Features A	10 (4.5)	4 (3.5)	14 (4.2)	1.303	0.400-4.251	0.199	0.655
Features B	0 (0.0)	0 (0.0)	0 (0.0)				
Features C	101 (45.7)	62 (54.4)	172 (51.3)	0.706	0.448-1.111	2.277	0.132
Criterion 3	221 (100.0)	114 (100.0)	335 (100.0)				

OR odds ratio with 95% confidence interval (CI), LR likelihood ratio and *p* value for the LR

DISCUSSION

The present study contributes to existing literature by obtaining that 3/4 of a university population had any class of joint hypermobility and 1/4 of them had generalized joint hypermobility, which is much higher than populations with different ages in the previous studies from Turkey [14-17, 22] and in line with the one study from America [23] (Table 5). Our low prevalence of peripheral joint hypermobility supported the view that this class, which is mainly non-pathological and affects small joints, is more common in children [20]. Generalized joint hypermobility, which is the presence of hypermobility simultaneously at upper, lower limbs, and axial skeleton, took second place in frequency ranking. Localized joint hypermobility, which is mainly in a single small or large joint, took first place in the ranking of frequency.

Joint hypermobility is usually accepted as non-symptomatic feature. Despite that, almost 50% of our participants with joint hypermobility were defined as hypermobility spectrum disorders when questioned. However, the frequency of hypermobility spectrum disorders was not reported before in literature due to its new definition [20]. None of studies from Turkey have reported hypermobile EDS (joint hypermobility syndrome or benign joint hypermobility syndrome) prevalence before. However, our results are in line with the findings of Russek and Errico and higher than the those found in two studies with a limited number of participants [24, 25] (Table 5). We found prevalence of hypermobile EDS according to different classificationsin the same participants group at a decreasing prevalence; 19.4%, 15.2%, and 1.2%, respectively. Main reason for this may be the lack of features B in our populations, information about the syndrome in young people's families (they were unaware of the existence of the syndrome), therefore, decision were made only in positivity of both features A and C. The another reason may be the fact that with the 2017 International Classification criteria, the joint hypermobility and secondary musculoskeletal problems were not adequate for the definition of a genetic syndrome, unless the interference of at least one different tissue or structure [20].

Most hypermobile and hypermobile EDSwere in female gender, which is also in line with the proposed association between sex and joint laxity [14, 16, 17, 23, 26, 27]. We found asymptomatic localized joint hypermobility in females, and localized hypermobility spectrum disorders in males at the highest prevalence. Arthralgia and back pain has been reported as the most common complaint in participants with generalized joint hypermobility[16]. In fact, stria in females (65.6%) and soft tissue problems in males (39.5%) were the most prevalent criteria for definition of joint hypermobility syndrome. These results are consistent with the view that the most frequent detected Brighton criteria for joint hypermobility syndrome are firstly dermal and secondly eye problems [28, 29]. Although the relationship of joint pain and generalized joint hypermobilityis still controversial in literature [14, 16,

Table 5. Prevelances in literature

Year, Authors	Evaluation	Participants count	Ages of population (years)	Beighton cut-off point	Definition	Females (%)	Males (%)	All (%)
2005, Seckin *et al.* [22]	Beighton	961	13-19	4/9	GJH	16.2	7.2	11.7
2005, Yildirim *et al*. [23]	Beighton	857	6-16	6/9	GJH	19.9	7.7	13.0
2006, Ofluoglu *et al.* [21]	Beighton	58 females	21-61	4/9	GJH	22	Nk	Nk
2013, Russek and Errico [31]	Brighton	290 female College athletes	Adolescent and College age	Nk	JHS	17.9	Nk	Nk
2015, Barcak *et al.* [20]	Beighton	437	11-18	5/9	GJH	12.4	6.1	9.1
2015, Sopper *et al.* [32]	Beighton	27 elite-level net ballers	14–26	4/9	GJH	Nk	Nk	63
	Brighton	27 elite-level net ballers	14–26		JHS	Nk	Nk	14.8
2016, Russek and Errico [26]	Beighton	267	17-26	4/9	GJH	51.0	27.4	40.1
	Beighton	267	17-26	5/9	GJH	36.7	13.7	26.2
	Brighton	267	17-26		JHS	24.5	13.7	19.5
Current study, Tuna	Beighton	335	18-25	4/9	GJH	41.6	21.9	34.9
	Beighton	335	18-25	5/9	GJH	33.0	12.3	25.9
	Brighton	335	18-25	4/9	JHS	24.0	10.5	19.4
	the 2017 IC	335	18-25		HSD	38.4	38.7	38.5
	the 2017 IC	335	18-25		hEDS	1.8	0	1.2

Nk = not known, GJH = generalized joint hypermobility, PJH = peripheral joint hypermobility, LJH = localized joint hypermobility, HSD = hypermobility spectrum disorder, hEDS = hypermobile Ehlers-Danlos syndrome, IC = International Classification

30], our low percentages of arthralgia can be due to the inclusion criteria (self-defined healthy in mean of non-painly). Based on our study, more than half of the participants with generalized joint hypermobility were "not healthy" when the Brighton criteria were applied. So as Albayrak *et al*. [30] stated; "symptoms other than pain may be overlooked during the examination of benign joint hypermobility syndrome patients unless they are specifically questioned".

Limitations

The present study has some limitations. Although, participants were questioned for history of use of dental braces with medical confirmation, first, the data of dental braces information is self-reported. It may not reflect the exact incidence of these. Second, there are only 18-25 year old participants in the study, which makes it difficult to extrapolate the results to entire populations. However, to the best of our knowledge,

this is the first study to analyze the prevalence in a university population of classified joint hypermobility as generalized, peripheral, and localized. In addition, to analyze the prevalence of hypermobility spectrum disorders and hypermobile EDS diagnosed according to three classifications in the same population.

CONCLUSION

In conclusion, joint hypermobility is quite common and nearly half of participants with joint hypermobility have hypermobility spectrum disorders. The difference between old and new classification results raised the needs of new researches in the area. We want to urge colleagues to consider carefully researching this group of patients in order to create opportunity for timely identify and resolve multisystemic complaints. We think that prevention of disabilty and avareness of the the multisystemic nature of syndroms starts with definition of generalized joint hypermobility and associated syndromes.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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