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Is there a difference in 25-hydroxyvitamin D levels between female university students with and without joint hypermobility?

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ABSTRACT

Objectives: Individuals with joint hypermobility (JH) constitute a sensitive group with regard to musculoskeletal problems. This study aimed to investigate whether females with generalized joint hypermobility (GJH) are at risk of hypovitaminosis D compared with non-GJH female participants and whether there is a relationship between vitamin D levels, Beighton score and musculoskeletal complaints.

Methods: In this cross-sectional, descriptive and case-control study, 76 female participants aged 18-25 years were included. The Beighton score with a cut-off of 4/9 was applied for defining GJH. In addition, serum biochemical (the enzymatic colorimetric method) and hormonal (the electrochemiluminescence method) parameters were evaluated.

Results: The mean serum 25-hydroxyvitamin D (25[OH]D) levels of GJH (n = 38) and non-GJH (n = 38) groups were 15.70 ± 7.96 ng/mL and 16.80 ± 5.45 ng/mL, respectively. There was no statistically significant difference between the groups in terms of biochemical and hormonal parameters. We found vitamin D deficiency in 89.5% of participants with GJH, and 84.2% of controls. There was no correlation between vitamin D, Brighton criteria, and musculoskeletal complaints.

Conclusion: The female participants with GJH showed similar frequency of musculoskeletal complaints and similar low level of 25(OH)D in relation to controls.

Keywords: female, joint hypermobility, musculoskeletal complaints, 25-hydroxyvitamin D deficiency

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Joint hypermobility or laxity is having a range of motion beyond the limits of normal joint. It can affect one or more joints. Beighton scoring (BS), where in nine joints are evaluated, is used to define JH and BS 4-6/9 is reported as generalized joint hypermobility (GJH) [1, 2]. Hypermobility brings with it many problems as musculoskeletal or systemic manifestations. Musculoskeletal manifestations are traumas, degenerative joint and bone diseases, disturbed proprioception, muscle weakness and musculoskeletal traits. Systemic manifestations are cardiovascular involvements, skin, mucosae, fascia involvement, and nervous system involvement [2]. These manifestations were included easily under the umbrella named hypermobility syndrome or hypermobile Ehlers-Danlos syndrome (hEDS) with Brighton criteria until the 2017

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International Classification of EDS that were based on strict criteria [3].

According to updated classification hEDS is a connective tissue disorder simultaneously comprised; 1) Beighton score ≥ 5/9, 2) At least two of of feature A (at least 5 meets of a 12 systemic features of a connective tissue), feature B (positive family history) and feature C (at least one existence of three musculoskeletal complications), and 3) Exclusion of extraordinary skin fragility, further connective tissue disorders, and another diseases with JH. However, feature B was accepted enough for the diagnosis [3].

Although Vitamin D is a hormone that is essential for functioning of muscles, as well as bone mineralization [4], until now, no study has reported vitamin D levels in GJH and its correlation with musculoskeletal complaints. Hypermobile EDS with GJH is reported as risk for chronic pain, fatigue [5], low bone density, osteoporosis, and fractures [6, 7]. While management suggestions include considering 25-hydroxyvitamin D (25[OH]D) deficiency, there is no enough data on levels of 25(OH)D in EDS groups as well as GJH [8-11]. Considering the possibility that individuals with GJH differ from controls in mean of level of 25(OH)D and some biochemical parameters (sodium, potassium, chlorine, alkaline phosphatase, calcium, phosphorus, magnesium, iron, and iron binding capacity levels) we aimed to evaluate them and comprise with controls.

METHODS

Patients

For the aims of this study, we selected females with definition of GJH according to the Beighton scoring, aged between 18-25 years. Participants were selected from a total of 221 female students from the Health Sciences Faculty of Trakya University (Edirne, Turkey). A group of students with Beighton score ≤ 3/9 and no any genetic disorder, chronic drug use and chronic disease of locomotor system was selected as control. All participant were selected from the same sources. Controls were matched by age and sex with individuals with GJH. Participants with a Beighton score of ≥ 4/9 were included in the GJH group and those with a score ≤ 3/9 were included in the control group (non-GJH) [12]. Exclusion criteria were male sex, drug use, and the presence of a known disease in both groups (Figure 1). Based on the mean 25(OH)D vitamin level 26.3 in the control group [13] and minimum difference between groups of 25%, an α error of 5%, SD of 10%, and power 80% we defined a sample of 38 participants for each group. This observational, cross-sectional (between February 2017 and July 2017), controlled, quantitative study was approved by the Ethics Committee of the Trakya University Medical Faculty (TÜTF-BAEK-2016/105) and written informed consent was obtained from each participants.

Edirne is city in the Marmara Region of Turkey, latitudes 40°30-42°00 North l and 26°00-27°00 East. Average maximum temperatures range between 6.5°C in winter and 31.7°C in summer, with annual average of 19.6°C [14].

Clinical Evaluation

A total of 221 female students from Health Science Faculty of Trakya University (Edirne, Turkey) underwent an initial clinical interview and Beighton scoring. Beighton scoring was performed by evaluating nine joints and the following items:

I- Placement of hands flat on the floor without bending the knees

II- Hyperextension of the elbow to ≥ 10°

III- Hyperextension of the knee to ≥ 10°

IV- Opposition of the thumb to the volar aspect of the ipsilateral forearm

V- Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90° [15]. During physical examination, we investigated the presence of features used in the diagnosis of hEDS according to the 2017 International Classification of EDS [3]. Data collected included age, sex, height, weight, BMI, clothing style, and history of musculoskeletal complaint. To evaluate history of the musculoskeletal complaint, participants were questioned aboutthe joint pain, widespread musculoskeletal pain and soft tissue injuries. Clothing style of the participants was registered by researchers based on their observations as veiled or not.

Laboratory Evaluation

After 10-12 h fasting, venous blood samples fromthe antecubital area were taken from all participants between 08.30 and 9.00 in the morning

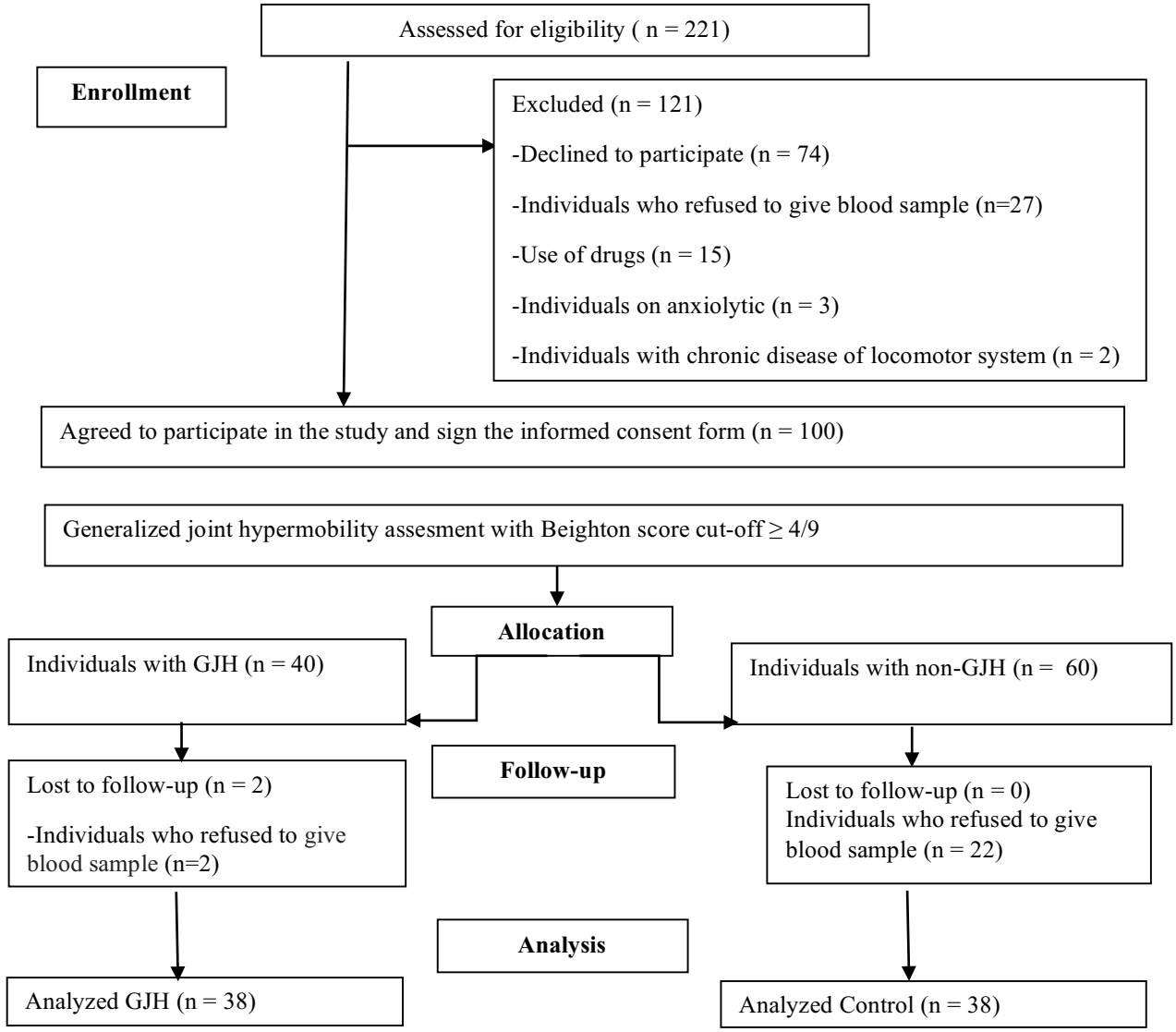

Figure 1. Flow diagram of the progress.

from April 2017 to May 2017. Serum sodium, potassium, chlorine, alkaline phosphatase, calcium, phosphorus, magnesium, iron, and iron binding capacity levels were measured using the enzymatic colorimetric method (Beckman Coulter AU 5800), and serum 25(OH)D, folic acid, and ferritin levels were evaluated using the electrochemiluminescence method (Beckman Coulter UniCelDxI 600). 25(OH)D levels of participants were classified according to the Endocrine Society asdeficiency (< 20 ng/mL), insufficiency (21-29 ng/mL), normallevels (30-39 ng/mL), and preferred levels (40-60 ng/mL) [16].

Statistical Analysis

Statistical evaluation was performed by the IBM SPSS version 20.0 statistics software package (IBM Corporation, Armonk, NY, USA). Descriptive variables were reported within groups according to frequency, means, standard deviation, and percentages. Normal distribution were evaluated by the Shapiro-Wilk test. T test was used for normally distributed data. Spearman's rho correlation analysis test was used to assess correlations between variables. A p value of < 0.05 was considered statistically significant.

Table 1. Characteristics of participants with GJH and controls

	Groups	n	Mean ± SD	*p* value
Age, year	GJH	38	19.87 ± 1.45	0.239
	Control	38	20.26 ± 1.44	
	Total	76	20.07 ± 1.45	
Height, m	GJH	38	1.65 ± 0.05	0.464
	Control	38	1.64 ± 0.04	
	Total	76	1.64 ± 0.05	
Weight, kg	GJH	38	56.31 ± 6.29	0.643
	Control	38	57.05 ± 7.45	
	Total	76	56.68 ± 6.86	
BMI, kg/m^2	GJH	38	20.63 ± 1.75	0.304
	Control	38	21.14 ± 2.44	
	Total	76	20.88 ± 2.13	
Veiled clothing style, %	GJH	9	23.7	0.079
	Control	7	18.4	
	Total	16	21.1	
History of musculoskeletal complaint, %	GJH	14	43.8	0.486
	Control	18	56.3	
	Total	32	42.1	
25 (OH)D level, ng/ml	GJH	38	15.73 ± 7.97	0.496
	Control	38	16.80 ± 5.46	
	Total	76	16.26 ± 6.81	

GJH = generalized joint hypermobility, BMI = body mass index

RESULTS

Complete laboratory data were obtained for 76 female participants, of whom 38 had GJH and 38 did not. Total Beighton score range were 0-9/9. The average ages of GJH and control groups were 19.87 ± 1.45 and 20.26 ± 1.44 years, respectively. Participants' age, height, weight, BMI, clothing style, and history of musculoskeletal pain parameters were normally distributed. The mean serum 25(OH)D levels of GJH and control groups were found no statistically different (Table 1). Laboratory data of sodium, potassium, chlorine, alkaline phosphatase, calcium, phosphorus, magnesium, and iron, were obtained for 73 participants, of whom 38 had GJH and 35 did not. There was no statistically significant difference between the GJH and control groups with respect to the biochemical and hormonal levels. Significant positive correlation was found between weight and 25(OH)D levels (Table 2). Neither in the GJH nor in the control group hEDS was identified.

Table 2. Correlations of parameters with statistically significance

		r	*p* value
Age	Chlorine	-0.277	0.020
	Phosphorus	0.287	0.014
	Hyperextension of right elbow	-0.229	0.046
	Hyperextension of right knee	-0.264	0.021
	Hyperextension of left knee	-0.252	0.028
Weight	Calcium	0.267	0.023
	Height	0.485	<0.001
	BMI	0.847	<0.001
25(OH)D levels	Weight (kg)	0.303	0.008
	Potassium	0.265	0.022
	Hyperextension of right elbow	-0.340	0.003
	Hyperextension of left elbow	-0.244	0.034

Distribution of participants according to 25(OH)D calassifications among the GJH and control groups was showed in Table 3. Only one of participants had preferred level of vitamin D.No correlation was found between the Beighton scores, musculoskeletal manifestations, and serum 25(OH)D levels. No correlation was found between the clinical parameters (Beighton scoring parameters) of participants with GJH and 25(OH)D levels, except for a statistically significant negative correlation between the 25(OH)D levels and the hyperextension of right and left elbow (Table 2).

Table 3. Distribution of 25(OH)D classifications among the groups

		n (% within groups)		
		GJH	**Control**	**Total**
25 (OH) D classification	Deficiency	34 (89.5)	32 (84.2)	66 (86.8)
	Insufficiency	2 (5.3)	4 (10.5)	6 (7.9)
	Normal	1 (2.6)	2 (5.3)	3 (3.9)
	Preferred	1 (2.6)	0 (0.0)	1 (1.3)
Total		38 (100)	38 (100)	76 (100)

GJH = generalized joint hypermobility

DISCUSSION

Present study shows that mean 25(OH)D levels are low, but not statistically different in females with GJH. We also found no statistically significant association between Beighton scoring and neitherhistory of musculoskeletal complaint nor 25(OH)D levels. While GJH is widely known as predisposing to musculoskeletal pain, neither vitamin D deficiency nor insufficiency is not sufficiently researched in this population. Significant positive correlation was found between weight, BMI and 25(OH)D levels. These results are not consistent with previous studies reporting negative correlation between BMI and vitamin D in healthy adults [17]. This wasprobably due to both groups having normal mean BMI.

The lack of association between 25(OH)D levels and musculoskeletal complaints was probably because of both groups having levels below normal limits. These results are uniform with other studies that also reported no association between these variables. In retrospective multicenter study on patients who applied to physical medicine and rehabilitation outpatient clinics with non-specific muscle pain, vitamin D deficiency was detected in 70.9% of patients (without information about whether patients are hypermobile or not). However, vitamin D deficiency in this population was reported not associated with the severity and duration of pain [18]. Hypermobility, vitamin D deficiency, and female sex are risk factors for idiopathic musculoskeletal pain [11]. Of these, hypermobility and female sex are structural unchanging factors. However, it is possible to misdiagnosed musculoskeletal pain associated with vitamin D deficiency as a pain syndrome associated with joint laxity or vice versa. There are limited number of publications on the role of 25(OH)D in hEDS, defined by the Brighton criteria, where GJH and various symptoms as joint pain are questioned together [6, 9, 19, 20]. Some publications suggest that vitamin D should be observed in painful individuals with hEDS [9, 20]. We found similar serum 25(OH)D levels between the groups and deficiency was found in 89.5% of participants with GJH, and 84.2% of controls. These findings are consistent with low vitamin D levels in eight of 14 cases with vascular type EDS with mean age of 37 ± 16 years [21]. Vitamin D levels < 30 ng/mL were reported to be similar in classical and hypermobility type EDS (86%) and control (82%) groups with a mean age of 40.3 ± 5.9 years. Mean serum 25(OH)D levels of individuals with classical or hypermobility type EDS have been reported as 20.2 ± 12.9 ng/mL [6].

The participants with GJH showed no higher frequency of musculoskeletal complaints in relation to control participants, refusing the profile waited for this population, according to the literature. It was probably due to 25(OH)D in both groups below the recommended levels.

Limitations

A potential limitation of this study was limited number of participants. Current study did not include questionnaires interesting in socioeconomic status and vitamin D intake in the diet. In addition, our study was mainly female student-based and the need to establish knowledge on GJH and hEDS require studies with large population.

CONCLUSION

The female participants with GJH showed similar frequency of musculoskeletal complaints and low 25(OH)D levels in relation to controls. The frequency of deficiency and insufficiency of 25(OH)D in current study is parallel to studies, reporting a high frequency of vitamin D below normal limits, even in places with plenty sunlight.

Conflict of interest

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

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