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THE ROLE OF INSULIN SENSITIVITY AND BODY MASS INDEX ON ORTHOSTATIC INTOLERANCE

İNSÜLİN DUYARLILIĞI VE VÜCUT KİTLE İNDEKSİNİN ORTOSTATİK İNTOLERANS ÜZERİNE ETKİLERİ

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Abstract

Objective: To assess the effects of insulin sensitivity and anthropometric measurements on orthostatic intolerance syndromes.
Methods: This is a retrospective study. Patients with history of syncope aged between 7-18 years were analyzed according to insulin sensitivity index and anthropometric measurements. Patients were grouped according to the head-up tilt test results (test positive and test negative). Also, patients who had positive tilt tests were divided into four subgroups such as vasodepressor vasovagal syncope (VVS), cardioinhibitory VVS, mixed VVS, and postural orthostatic tachycardia syndrome.
Results: A total of 509 patients were included in the study. The mean age was 13.45 ± 2.82 years, and %64.4 were girls. The tilt test was positive in 214 patients and negative in 295. With the tilt test results, 173 patients were diagnosed with VVS and 41 patients (19 %) with POTS. There were no statistically significant difference between the groups according to the insulin sensitivity indices. In anthropometric measurements, a significant difference was observed between the two groups in height, height standard deviation score (SDS), BMI SDS and BMI *p* (*p* =0.008, *p*= 0.02, p=0.036, *p*=0.03, respectively).
Conclusion: In our study, while the low BMI and being tall were the predisposing factors for VVS episodes especially in young girls, there was no relationship between the insulin sensitivity indices and positive head-up tilt test result. Providing appropriate treatment by shedding light on factors that cause recurrent syncope can contribute to the quality of life of patients.

Keywords: *Syncope, postural tachycardia syndrome, vasovagal syncope, head-up tilt test.*

Öz

Amaç: Çalışmanın amacı insülin duyarlılığı ve antropometrik ölçümlerin ortostatik intolerans sendromları üzerindeki etkilerini değerlendirmektir.
Yöntem: Retrospektif bir çalışmadır. 7-18 yaş arası senkop öyküsü ile başvuran hastalarda insülin duyarlılık indeksleri hesaplandı ve antropometrik ölçümlerine değerlendirildi. Hastalar head-up tilt test sonuçlarına göre test pozitif ve test negatif olarak gruplandırıldı. Ayrıca tilt testi pozitif olan hastalar vazodepresör vazovagal senkop (VVS), kardiyoinhibitör VVS, mikst VVS ve postural ortostatik taşikardi sendromu olmak üzere dört alt gruba ayrıldı.
Bulgular: Çalışmaya toplam 509 hasta dahil edildi. Yaş ortalaması 13,45 ± 2,82 yıldı ve %64,4'ü kızdı. Tilt testi 214 hastada pozitif, 295 hastada negatifti. Tilt testi sonuçları ile 173 hastaya VVS ve 41 hastaya (%19) POTS tanısı konuldu. İnsülin duyarlılık indekslerine göre gruplar arasında istatistiksel olarak anlamlı fark yoktu. Antropometrik ölçümlerde boy, boy standart deviasyonu, vücut kitle indeksi (VKİ) standart deviasyonu ve VKİ persentili (sırasıyla p=0,008, *p*=0,02, *p*=0,036, *p*=0,03) açısından iki grup arasında anlamlı farklılık gözlendi.
Sonuç: Çalışmamızda özellikle genç kızlarda düşük VKİ ve uzun boylu olmak vazovagal senkop ataklarına zemin hazırlayan faktörler iken, insülin duyarlılık indeksleri ile pozitif head-up tilt test sonucu arasında ilişki bulunmadı. Tekrarlayan senkoplara neden olan faktörlere ışık tutarak uygun tedavinin sağlanması hastaların yaşam kalitelerine katkı sağlayabilir.

Anahtar Kelimeler: *Senkop, postural taşikardi sendromu, vazovagal senkop, head-up tilt testi.*

Introduction

The autonomous nervous system, blood volume, and skeletal as well as respiratory muscle are essential for cardiovascular adaptation when standing upright. Of all the emergency cases in the US, %1.5 are due to syncope and of these, orthostatic intolerance (OI) syndromes are the most common causes of non-cardiac syncope. It is important to distinguish between reflex and cardiogenic syncope. We can define OI as the inability to tolerate an upright posture due to insufficient blood volume or defective sympathetic adrenergic activity. Different orthostatic intolerance syndromes have been described, especially postural orthostatic tachycardia syndrome (POTS) and vasovagal syncope (VVS).[1,2] Common causes of POTS are, a partial denervated circulatory system, insufficient blood volume, or a hyperandrogenic state.[3,4]

The factors that cause a predisposition to VVS and postural tachycardia syndrome are not fully known. Previous studies have focused on gender, age, body mass index (BMI), hypovolemia, sex hormones, and many other factors in the adult age group.

In addition to its metabolic effect, insulin is known to influence the autonomic nervous system and the vascular skeletal muscles. Some authors have observed that insulin infusion causes sympathetic discharge and muscular vasodilation, and this effect occurs not secondary to the metabolic effect but in parallel with it. The direct vasodilator effect of insulin is especially evident in the terminal arterioles in the lower limb muscles.[5,6] The gold standard used to evaluate insulin sensitivity is the hyper insulinemic-euglycemic clamp method, but because this method is difficult and expensive, there are simpler methods such as HOMA-RI, 1 / HOMA, G0 / I0, G0xI0, and QUICKI indexes that originate from plasma glucose and insulin values. People who have had VVS are thought to have high insulin sensitivity. On the other hand, increased intracellular fat accumulation increases insulin resistance. Therefore, it can be predicted that a high BMI value can be a protective factor against syncope.[7-9]

There are not many studies on children related to this clinical condition, which obviously cannot be associated with a single pathophysiological mechanism. Also, the role of insulin and BMI in hemodynamics as a predisposing factor has not been adequately studied in orthostatic intolerance syndromes such as VVS and POTS. There are fewer studies on this subject in children and adolescents. This study aims to evaluate the effect of insulin sensitivity and BMI on OI syndromes.

Methods

The study was conducted on 509 children with syncope and presyncope who were evaluated with Head-up tilt table test (HUTT) between December 2011and January 2020. Patients were not included if they had chronic illnesses or any cardiac or neurological pathology. A comprehensive history, physical examination findings, and laboratory tests were obtained from the patient files. For evaluating insulin sensitivity, the following parameters were calculated in 320 patients whose serum insulin (I0) and fasting glucose (G0) levels were recorded.

1. Indices obtained from fasting glucose and insulin level: G0 / I0 and G0 X I0
2. HOMA-RI (Homeostatic model assessment for insulin resistance): I0 X G0 /22.5
3. 1 / HOMA
4. QUICKI (Quantitative insulin sensitivity check index): 1 / [log (I0) + log (G0)]

Electrocardiography, echocardiography, and tilt test results were examined. Patients' sex, age, height, weight, BMI and vital signs at the beginning and end of the tests were recorded. Baseline 12 lead ECGs were taken at rest in the supine position with the Nihon Kohden ECG machine, with paper speed of 25 mm/s and voltage sensitivity of 10 mm/mV.

Tilt Table Test Protocol

Before the test, the drugs that affect the cardiovascular system and thus interfere with the test, were discontinued; and the test was performed after 3 hours of fasting. An intravenous catheter was placed 30 minutes before starting the test which was initiated after the patients rested in a quiet room for 20 minutes in a lying position. In the drug-free passive phase, the table was tilted to 70 degrees and the patients were observed for 20 minutes. Continuous ECG monitoring was performed throughout the test. Blood pressure, oxygen saturation, and heart rate were measured every five minutes. For patients with no symptoms, at the end of the first phase, we initiated the second phase with nitroglycerin provocation. In the second active phase, sublingual nitroglycerin was given to these patients after resting in supine position for 10 minutes and the active phase was initiated by tilting the table back to the 70-degree angle position. Blood pressure, saturation and heart rate were measured in 5-minute intervals until syncope occurred. In the event of syncope, presyncope, hypotension, bradycardia, or inability to continue the test, the table was tilted back to 0 degrees and the test was terminated. All measurements during the procedure were recorded.

Hemodynamic responses of the test were evaluated according to the European Cardiology Guideline and VVS and POTS were diagnosed accordingly. Postural Orthostatic Tachycardia Syndrome: included in this group were patients whose heart rate exceeded 120/min without hypotension within the first 10 minutes after standing up from the supine position, or patients with a 40/min increase in heart rate compared to the baseline. VVS were classified according to the classification of the Vaso-Vagal Syncope International Study (VASIS):

Type 1 (mixed type): Included in this group were patients with bradycardia, hypotension, and no decrease in heart rate below 40 beats per minute during syncope for more than 10 seconds. In these patients, asystole for less than 3 seconds can be seen and the blood pressure decreases before the heart rate.

Type 2A (cardioinhibitory type without asystole): This group consisted of patients whose heart rate decreased below 40 beats for longer than 10 seconds during syncope, who had asystole for less than three seconds and whose blood pressure decreased before the heart rate.

Type 2B (cardio inhibitor with asystole type): This was the group of patients whose blood pressure decreased below 40 seconds longer than 10 seconds and who developed asystole for more than three seconds (blood pressure decreases at the same time or earlier than heart rate).

Type 3 (vasodepressor type): This final group was composed of patients whose heart rate did not decrease more than 10% of the baseline value even when the syncope was most prominent and whose blood pressure drop was very evident.

We divided the patients with syncope complaints into two groups as negative and positive according to their tilt test results. Patients with positive tilt test results were divided into four subgroups as vasodepressor type VVS, cardioinhibitory type VVS, mixed type VVS, and POTS.

All procedures performed involving human participants were in accordance with the ethical standards of the local ethics committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by the local ethics committee of Kocaeli University Research and Application Hospital (KAEK/2011/46). Due to the retrospective nature of the study, written informed consent forms were not obtained.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and MedCalc for Windows, version 19.2.0 (MedCalc Software, Ostend, Belgium). Shapiro-Wilk's test was used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean ± standard deviation or (in case of no normal distribution) median (25th-75th percentile). Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were carried out using independent samples t-test/ Mann-Whitney U test, whichever was appropriate. Associations between continuous variables were determined by Pearson and Spearman correlation analyses and the association between two categorical variables was examined by the Chi-square test. ROC analysis was used to determine area under the ROC curve (AUC) and cut-off values. All statistical analyses were carried out with 5% significance and a two-sided *p* value<0.05 was considered statistically significant.

Results

Of the 509 patients included in the study, 181 were male (35.6 %), 328 were female (64.4%) that the female/male ratio was 1.76. The mean age was 13.43 ± 2.7 years (7-18). The HUTT was positive in 214 (41.2%) of the patients (59.2% were female and 40.8% were male) with an mean age of 13.4±2.7 years. With the tilt test 104 patients (48.6 %) were diagnosed with mixed type VVS, 41 patients (19%) with POTS, 35 patients (16.4%) with cardioinhibitory type, and 34 patients (16%) with vasodepressor type VVS. In 295 patients, the tilt test was negative. There was no statistical difference between the positive and negative HUTT groups regarding mean age (p = 0.881) (Table 1).

Whereas there was no significant difference between the positive and negative HUTT groups in terms of the mean systolic and diastolic blood pressure measured at the beginning of the test, mean of basal heart rate was significantly lower in the HUTT positive group (p=0.013). No statistically significant difference was observed in the comparison of the two groups in terms of weight, weight standard deviation score (SDS), BMI. However, there was a significant difference in height, height SDS, BMI SDS and BMI p (p=0.008, p=0.02, p=0.036, p=0.03, respectively) (Table 1). HOMA, 1 / HOMA, G0 / I0, G0xI0, QUICKI index values used in the study of insulin sensitivity were not different between the two groups (Table 2).

We evaluated the difference in terms of demographic characteristics and physical examination findings between the 41 patients diagnosed with POTS, 174 patients diagnosed with VVS, and the HUTT negative group. In the POTS group, the median height and the height SDS value was higher than the other two groups (p=0.001, p=0.001, respectively). It was observed that the mean height and height SDS values were close to each other in the VVS and HUTT negative groups. While there was no significant difference between the three groups in terms of the BMI, the mean BMI percentile was lower in the POTS group (p=0.03). Basal heart rate, basal systolic and diastolic blood pressures were similar among the three groups (p=0.149, p=0.137, p=0.130, respectively) (Table 3).

Table 1. Clinical characteristics and physical examination findings of patients

	HUTT negative (n:295) Mean±Sd	**HUTT positive (n:214) Mean±Sd**	***p***
Age	13.4±2.9	13.4±2.7	0.881
Weight (kg)	49.6±15.7	50.1±14.6	0.376
Weight SDS	-0.2±1.4	-0.5±4.6	0.470
Height (cm)	154.8±15.2	158.6 ±14.6	**0.008**
Height SDS	-0.18±1.3	0.19±1.3	**0.002**
BMI (kg/m2)	20.2±4.11	19.5±3.64	0.130
BMI SDS	-0.17±1.41	-0.43±1.29	**0.036**
BMI p	46.55±33.5	38.48±31.3	**0.030**
Baseline SBP (mmHg)	118.1±16.87	115.6±13.92	0.096
Baseline DBP (mmHg)	67.5 ±10.1	65.8 ±.10	0.043
Baseline Heart Rate (bpm)	86.92 ± 15.4	83±14.2	**0.013**

HUTT: Head-up Tilt Test, VVS: Vasovagal syncope, POTS: Postural orthostatic tachycardia syndrome, BMI: Body mass index, HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Table 2. Insulin sensitivity indices in patients with HUTT negative and positive

	HUTT negative (n:208) Mean±Sd	**HUTT positive (n=112) Mean±Sd**	***p***
Insulin Level (mIU/ml)	10.5±9.08	9.54±7.63	0.269
Glucose (mg/dl)	77.17±11.6	78.25±10.14	0.272
HOMA-RI	-1.85±1.87	1.71±1.58	0.703
1/HOMA	1.01±1.07	0.99±1	0.875
G0/I0	9.81±8.66	10.66±8.43	0.155
G0xI0	749.49±758.25	696.263±641.72	0.704
QUICKI	0.363±0.044	0.365±0.042	0.571

HUTT: Head-up Tilt Test, HOMA-RI: Homeostatic model assessment for insulin resistance, G0/I0: fasting glucose level / fasting insulin level, G0xI0: fasting glucose level x fasting insulin level, QUICKI: Quantitative insulin sensitivity check index.

Table 3. Comparison of demographic, characteristics, and physical examination findings of patients according to HUTT.

	POTS (n:41) Mean±Sd	**VVS (n:173) Mean±Sd**	**Tilt (-) (n:205) Mean±Sd**	***p***
Age	14.07±2.4	13.29±2.7	13.41±2.97	0.301
Weight (kg)	50.9±11.9	50.0±15.23	50.0±15.88	0.685
Weight SDS	-1.83±9.9	-0.20±1.43	-0.19±1.48	0.885
Height (cm)	163.7±13.7	157.3 ±14.2	155.02 ±15.3	**0.001**
Height SDS	0.65±1.19	0.07±1.31	-0.18±1.39	**0.001**
BMI (kg/m2)	18.7±2.48	19.76±3.9	20.2±4.15	0.094
BMI p	27.33±24.7	41.12±32.03	46.55±33.7	**0.003**
BMI SDS	-0.81±1.08	-0.34±1.33	-0.17±1.41	**0.016**
Baseline SBP (mmHg)	114.80±11.4	116.2±14.6	118.35±16.9	0.137
Baseline DBP (mmHg)	64.5±7.2	66.8±8.89	67.69±10.1	0.130
Baseline Heart Rate (bpm)	82.71 ± 13.6	83.91±14.6	86.74±15.44	0.149

HUTT: Head-up Tilt Test, VVS: Vasovagal syncope, POTS: Postural orthostatic tachycardia syndrome, BMI: Body mass index, HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

A ROC curve was used to detect the predictive value of BMI SDS. The AUC was 0.606, with a 95% CI of 0.537 to 0.672. The cutoff value to differentiate between POTS and VVS groups was -4.46, which produced a sensitivity of %51.22 and a specificity of 68.02%. The second ROC curve was used to detect the predictive value of height SDS and showed that the AUC was 0.609, with a 95%CI of 0.540 to 0.675. A height SDS of 2.95 was stated to be the cutoff value to discriminate between POTS and VVS, which produced a sensitivity of 87.80%, and a 38.57% specificity (Figure 1).

In females, mean BMI SDS, BMI p, baseline systolic blood pressures were significantly lower in the POTS group (*p*=0.01, 0.004, 0.036, respectively), and height SDS was significantly higher **(***p*=0.004). There was no significant difference between the groups in terms of mean age, weight SDS, basal heart rate, and diastolic blood pressure in females. In males, means of all variables were similar among the three groups. In patients with VVS and POTS, there were no significant differences between the two sexes in terms of age, BMI SDS, BMI p, height SDS, weight SDS, basal heart rate, basal systolic and diastolic blood pressures (Table 4).

The tilt test was positive in 43.3% of the underweight patients, negative in 56.7%, and there was no significant difference in the underweight patients with the Pearson chi-square test in terms of tilt test positivity compared to other patients (Pearson chi-square test *p*=0.232). 10% of underweight patients had POTS, and 33.3% had VVS. Each groups' tilt test results did not differ according to the BMI subgroups (for Pearson Chi-square test *p*=0,158). While there was a single overweight patient in the POTS group, there were no obese patients (Table 5).

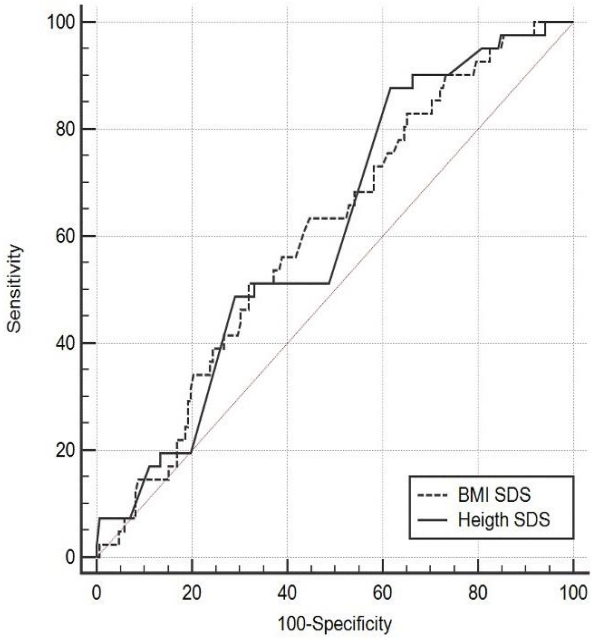

Figure 1. A ROC curve showed the cutoff value of Body Mass Index SDS to differentiate POTS and VVS was -4.46 and predictive value of height SDS was 2.95.

Table 4. Clinical characteristics and physical examination findings of patients according to HUTT and sex

		VVS	POTS	HUTT Negative	*p*
Age	Female Male *p*	13.54±2.69 12.91±2.86 0.142	14.46±2.37 13.53±2.42 0.23	13.75±2.79 12.72±3.21 0.013	0.301 0.744
BMI SDS	Female Male *p*	-0.39±1.38 -0.27±1.24 0.878	-0.78±1.23 -0.85±0.87 0.84	-0.23±1.42 -0.49±1.33 0.008	**0.01** 0.272
BMI p	Female Male *p*	41.05±31.00 41.22±33.79 0.976	27.83±25.99 26.65±23.82 0.95	50.19±34.38 38.85±31.07 0.010	**0.004** 0.277
Height SDS	Female Male *p*	0.17±1.25 -0.08±1.40 0.20	0.66±1.36 0.64±0.95 0.96	-0.21±1.35 -0.12±1.47 0.59	**0.004** 0.122
Weight SDS	Female Male *p*	-0.19±1.55 -0.23±1.24 0.929	-0.31±0.76 -3.97±15.49 0.78	-0.07±1.49 -0.44±1.43 0.043	0.647 0.462
Supine HR (bpm)	Female Male *p*	84.89±15.35 82.22±13.18 0.189	85.08±11.74 79.35±15.54 0.18	89.75±15.56 80.44±13.20 0.00	0.051 0.629
Supine SBP (mmHg)	Female Male *p*	115.6±13.94 117.1±15.75 0.477	114.3±10.33 115.4±12.94 0.77	119.3±14.19 116.2±21.48 0.210	**0.036** 0.973
Supine DBP (mmHg)	Female Male *p*	67.73±9.20 64.78±8.08 0.05	66.17±6.61 63.29±7.98 0.21	68.79±9.88 65.40±10.43 0.007	0.269 0.69

HUTT: Head-up Tilt Test, VVS: Vasovagal syncope, POTS: Postural orthostatic tachycardia syndrome, BMI: Body mass index, HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Table 5. HUTT results according to Body Mass Index.

	POTS	VVS	Tilt Testi Negative
BMI Underweight BMI ≤ 5p (n=60)	10 % (6)	33.3 % (20)	56.7% (34)
BMI Normal BMI 5p-84p (n=354)	9.6 % (34)	34.7 % (123)	55.6 % (197)
BMI Overweight BMI 85p-94p (n=48)	2.1 % (1)	31.3 % (15)	%66 (32)
BMI Obese BMI ≥ 95p (n=47)	0	31.9 % (15)	68.1 % (32)

BMI: Body Mass Index, POTS: Postural orthostatic tachycardia syndrome, VVS: Vasovagal syncope, HUTT: Head-up Tilt Test

Discussion

Orthostatic intolerance is common at all ages. In 15% of children, syncope will develop at least once until the end of adolescence. The etiology and factors affecting the recurrence risk of syncope in children remain uncertain. It is therefore important to identify factors that will predispose to syncope. The effects of many factors such as age, gender, basal heart rate, basal blood pressure, anthropometric measurements, fluid deficiency, level of physical fitness and sex hormone levels in adults have been evaluated in the previous studies.[10] Many studies investigating the effect of gender have revealed the dominance of females. In the analysis made by Deveau et al. from POST's data (prevention of syncope trials) I and II, it was found that 66 % of the 418 patients included in the study were women.[11]

Whereas VVS has been studied more, POTS which is an entity defined relatively recently, is a less understood orthostatic intolerance syndrome. The frequency of POTS is 0.02%, and its etiology is multifactorial. Many patients are between the ages of 15-25, and 75% of the affected individuals are women.

Autonomous denervation, hypovolemia, increased hyperadrenergic stimulation, poor physical condition, hypervigilance, baroreceptor anomalies, mast cell activation have been blamed in pathogenesis.[12,13] It is noteworthy that in 70% of patients with POTS the blood volume was decreased, plasma renin activity and aldosterone levels were found to be low while the level of angiotensin was high compared to healthy individuals[13]. Hyperadrenergic status occurs in 50% of cases. Increased sympathetic system activity is blamed, and attacks can also be triggered by physical activity and emotional stress.

In accordance with relevant literature, 59.2% of the patients who were found to have a positive tilt test in our study were female. In POTS patients, female dominance was more prominent, and 75% of the cases were women. Female sex is undoubtedly an independent risk factor for having a syncope attack. Although it is not known why POTS is more common in females, it is thought that there may be differences in the discharge of sympathetic nerves in muscles.[12,14] Among the studies which evaluated the effects of basal systolic and diastolic blood pressure and heart rate on syncope development, some argue that the risk of syncope is higher in patients with low systolic blood pressure.[15] In our study, in patients with positive tilt test, basal diastolic blood pressure and basal heart rate were found to be significantly lower rather than basal systolic blood pressure when compared to the HUTT negative group.

Effects of Body Weight Status on OI

The state of body weight appears to be an important factor that alters the orthostatic response and affects the tendency to non-cardiac syncope.[10] Many studies have shown that the lower the weight, the higher the susceptibility to orthostatic intolerance with down-regulation in the sympathetic system and up-regulation in the parasympathetic system. In a study by Christou *et al.*[10], individuals with low BMI were found to have low systolic, diastolic, and mean blood pressures during the test, which was thought to be a predisposing factor for syncope. Also, a positive correlation was found between BMI and total peripheral resistance, and it was stated that increased total peripheral resistance in individuals with high BMI could protect patients against syncope development while standing. It has been shown by Lin *et al,* that BMI is lower in POTS patients compared to patients diagnosed with VVS and healthy adolescents and emphasized it is a significant marker in the differential diagnosis of POTS and VVS.[5] It was also stated that patients with a BMI <19.3 were more likely to have POTS.[5] Syncope susceptibility of patients diagnosed with POTS with a low BMI has been attributed to a decrease in cardiac output due to hypovolemia and cardiac atrophy. Straznicky et al. detected a decrease in vascular resistance, especially in calves and suppression of sympathetic system activity, especially in patients who were on a low carbohydrate diet for four months without changing salt intake. The authors argued that the suppression of the sympathetic system in these patients contributed to orthostatic intolerance by causing inappropriate vasodilation in the lower limbs.[16] Yamada *et al.* found that low BMI and low systolic blood pressure in men are associated with a high incidence of VVS in 119 university students who experienced syncope during blood drawing.[7]

Although genetic studies are not clear, VVS is thought to have a genetic origin. In a study by Sheldon *et al.*, 12 possible variants that may be related to VVS were studied, three genes effective in serotonin signaling were detected, and it was emphasized that the majority of the affected patients were women.[17]

Effects of insulin sensitivity on OI

There is substantial evidence that insulin stimulates blood flow in the skeletal muscle and lowers vascular resistance. The results achieved separately both by Laasko and Anderson made it clear that euglycemic hyperinsulinemia at high physiological concentrations stimulates blood flow in muscle tissue in lean individuals. This stimulation is related to insulin's effect rather than the carbohydrate mechanism. Although insulin-induced vasodilation was reported in the majority of studies, but not all researchers found the same result. In addition, results of the studies on local insulin infusion leading to vasodilation are also contradictory. In healthy persons, insulin-induced vasodilation mainly occurs through nitric oxide release. Some authors stated that by inhibiting the alpha-2 adrenergic effect, they reduced the vasoconstrictor response to orthostatic stress.[6] It has been observed that insulin causes hypotension in patients with autonomic insufficiency. The importance of insulin in blood pressure regulation has been demonstrated by hypotension caused by unopposed insulin-induced vasodilation in patients with autonomic insufficiency. In a study by Ruiz *et al.*[6] which evaluated 13 young female patients, basal insulin and glucose levels were significantly lower in those diagnosed with VVS. G0 / I0, G0xI0, HOMA, 1 / HOMA, QUICKI, and ISI values which are parameters used to evaluate insulin sensitivity were found to be significantly different in the VVS group than the control group. In our study, there was no significant difference between the orthostatic intolerance group and the HUTT negative group in terms of G0 / I0, G0xI0, HOMA, 1 / HOMA, QUICKI parameters. While only 13 women were included in the study of Ruitz *et al*., 320 (112 HUTT positive vs 208 HUTT negative) patients were evaluated in our study. We believe that the difference between the two studies may be due to the limited number of cases in the previous study. In the research by Ruitz *et al.*, patients in the tilt test positive, negative, and control groups had equal baseline blood pressure readings, whereas the VVS group had a considerably lower basal heart rate.[6]

Limitations

The current study was unable to establish a link between insulin sensitivity and vasovagal syncope. Puberty is a period

of significant metabolic and hormonal adjustment. Notably, puberty is linked to a significant decline in insulin sensitivity. In healthy adolescents, insulin sensitivity reaches a trough in mid-puberty and subsequently rebounds after puberty completion. As the patients in our study were not all in the same pubertal stage, it is not possible to say that there is no relationship between insulin sensitivity and VVS.

Conclusion

There are a limited number of studies evaluating the impact of anthropometric and insulin sensitivity parameters on syncope in children. Our study established a link between the tendency to orthostatic intolerance syndromes and anthropometric parameters, particularly height and a low BMI percentile**.**

Conflict of Interest

The authors has no conflicts of interest.

Compliance with Ethical Statement

Ethics Committee approval for this research was obtained from the Local Ethics Committee for Kocaeli University, (dated December 25, 2019, no. 2O19/368).

Author Contributions

E.Z.B, G.A, K.B: The hypothesis of the study and desing; E.Z.B, D.K: Project development; E.Z.B, D.K, G.A, K.B: Literature search; E.Z.B, D.K, K.B: Analysis; E.Z.B, D.K, G.A, K.B: Manuscript writing; E.Z.B, D.K, G.A, K.B: Critical review.

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