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The relationship between cardiometabolic risks and vitamin D levels with the degree of obesity

Şişmanlığın derecesi ile kardiyometabolik riskler ve vitamin D düzeyi arasındaki ilişki

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Abstract

Aim: The aim of this study was to evaluate the cardiometabolic risk factors including vitamin D levels according to the degree of obesity in adolescents.

Material and Methods: This is a retrospective cross-sectional study. A total of 363 overweight/obese adolescents aged between 11 and 18 years who were evaluated in our clinic from January 2012 to December 2015 were included in the study. The degree of obesity was calculated as the body mass index standard deviation. Hypertension, dyslipidemia, hyperinsulinemia, hyperglycemia, insulin resistance, and vitamin D deficiency were defined as cardiometabolic risk factors. Mann-Whitney U, Chi-square, Spearman and Pearson's correlation tests, and linear regressions analyses were used for statistical analyses.

Results: Of the 319 (n=319/363) adolescents, all of whose cardiometabolic risk factors were known, 267 (85.7%) had at least one cardiometabolic risk factor. The body mass index standard deviation had a positive correlation with the number of cardiometabolic risk factors (p<0.001). In the linear regression models in which sex and age were considered as covariates, an increase of one unit in the body mass index standard deviation led to an increase of 6.085 mm Hg in systolic blood pressure, 4.4 mm Hg in diastolic blood pressure, 1.59 points in HOMA-IR, 13% in insulin level, and a decrease of 2.16 ng/mL in vitamin D levels.

Conclusion: In adolescents, the number of cardiometabolic risk factors increases as the degree of obesity increases. The determination of the severity of obesity can help to identify individuals at greater risk for higher blood pressure, impaired glucose metabolism, and lower serum vitamin D levels. On the other hand, the degree of obesity may not reflect the presence of abnormal lipid and glucose levels.

Keywords: Adolescents, cardiometabolic risk factors, degree of obesity, vitamin D level

Öz

Amaç: Bu çalışmanın amacı ergenlerde obezite derecesine göre D vitamini düzeylerini içeren kardiyometabolik risk etmenlerini değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma geriye dönük kesitsel bir çalışmadır. Çalışmaya Ocak 2012–Aralık 2015 tarihleri arasında kliniğimizde değerlendirilen 11–18 yaş aralığında toplam 363 aşırı ağırlıklı/şişman ergen alındı. Şişmanlığın derecesi beden kitle indeksi standart sapması olarak hesaplandı. Hipertansiyon, dislipidemi, hiperinsülinemi, hiperglisemi, insülin direnci ve vitamin D eksikliği kardiyometabolik risk etmenleri olarak tanımlandı. İstatistiksel çözümlemelerde Mann-Whitney U, Ki-kare, Spearman ve Pearson korelasyon testleri ve linear regresyon çözümlemeleri kullanıldı.

Bulgular: Tüm kardiyometabolik risk etmenleri bilinen 319 (n=319/363) ergenin 267 (%85,7) en az bir kardiyometabolik risk etmenine sahipti. Beden kitle indeksi standart sapması, kardiyometabolik risk etmeni sayısı ile aynı yönlü ilişki gösterdi (p=0,0001). Cinsiyet ve yaşın eş değişkenler olarak kabul edildiği linear regresyon modellerinde, beden kitle indeksi standart sapmasındaki bir birimlik artış, sistolik kan basıncında 6,085 mmHg, diyastolik kan basıncında 4,4 mmHg, HOMA-IR'de 1,59 puanlık, insülin seviyesinde %13'lük artışa; 25 hidroksi D vitamini seviyesinde 2,16 ng/ml azalmaya yol açıyordu.

Çıkarımlar: Ergenlerde, obezite derecesi arttıkça kardiyometabolik risk etmeni sayısı artmaktadır. Şişmanlığın ciddiyetinin belirlenmesi, daha yüksek kan basıncı ve bozulmuş glukoz metabolizması ve daha düşük serum D vitamini seviyeleri için daha fazla risk altında olanları belirlemede yardımcı olabilir. Diğer taraftan obezite derecesi anormal lipid ve glukoz düzeylerinin varlığını yansıtmayabilir.

Anahtar sözcükler: D vitamini düzeyi, ergenler, kardiyometabolik risk etmenleri, şişmanlığın derecesi

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Introduction

The frequency of overweight and obesity is gradually increasing worldwide (1). According to the data of World Health Organization, the prevalence of overweight and obesity among children and adolescents aged 5–19 years rose dramatically from just 4% in 1975 to just over 18% in 2016 (1). Numerous studies showed that among overweight or obese children and adolescents, cardiometabolic risk factors were more prevalent than those of their normal weight peers (2–5). However, the use of only a single category for obesity does not take into account the varying severity of obesity. It was also shown in some studies that more severe forms of obesity were associated with a greater immediate risk of complications related to weight, including abnormal lipid and blood glucose levels, and increased blood pressure levels; however, the definitions of severe obesity that were used in these studies were variable (3, 5, 6). Vitamin D also appears to play an important role in cardiovascular health (7–10). In the literature, it was shown that obesity, central obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol, insulin resistance, and metabolic syndrome were all associated with increased odds of having low 25 hydroxy vitamin D (25-OH vit D) levels after adjustment for age, sex, and Tanner stage (9). Obesity during childhood increases the risk of long-term obesity, as well as the risks of substantial complications and death in adulthood (11–13). Severe obesity at age 18 years was found to be independently associated with increased risk of diabetes and hypertension in adulthood (14). Thus, it is crucial to study the relationship between severity of obesity and cardiometabolic risk factors including vitamin D level during adolescence.

The aim of this study was to improve the understanding of the distribution of cardiometabolic risk factors including serum 25-OH vit D levels according to the degree of obesity, and to investigate the relationships between cardiometabolic risk factors and the degree of obesity in Turkish adolescents by sex.

Material and Methods

We obtained data retrospectively from the medical records of overweight or obese adolescents aged 11 to 18 years who attended Cerrahpaşa Medical Faculty, Department of Pediatrics, Adolescent Outpatient Clinic from January 2012 to December 2015 to evaluate the association between cardiometabolic risk factors including vitamin D status with the degree of obesity. Ethics committee approval was obtained for the study (Faculty Deanship Clinical Research Ethics Committee, Date: 20.06.2016; Number: 29430533-604.01.01-225233). The study was conducted in accordance with the principles of the 2008 Declaration of Helsinki. During this period, a total of 8311 new patients presented to the clinic. Among these, 363 obese or overweight adolescents who met the overweight and obesity criteria established by Cole et al. (15) according to age and sex, who were in puberty and had no chronic disease, and whose laboratory test results required the initial differential diagnosis of exogenous obesity [e.g. blood cortisol level, thyroid-stimulating hormone (TSH), free thyroxine (T4) levels] could be obtained, were included in the study. Blood cortisol level, TSH, and free T4 levels were not included in further analysis. Age, sex, weight, height, blood pressure, total cholesterol, triglyceride, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood glucose, insulin, and 25-OH vit D levels of the participants were recorded from the patients' files.

Weight status was classified on the basis of measured height and weight obtained at the time of physical examination, and body mass index (BMI) was calculated using the following formula: BMI = [weight / height^2 (kg/m^2)] (1). According to Cole's criteria, BMI values between the 85th and 95th percentiles were accepted as overweight, and BMI values above the 95th percentile were accepted as obese (15). The degree of obesity was calculated as the SDS-BMI by using age and sex-specific Turkish BMI percentiles, which were generated by using the LMS method, to standardize the degree of obesity (15, 16). The LMS method provides a way of obtaining normalized growth centile standards, which simplifies the assessment of growth standards and summarizes the data in terms of three smooth age-specific curves called L (lambda), M (mu), and S (sigma) (15).

Hypertension, dyslipidemia, hyperinsulinemia, hyperglycemia, insulin resistance, and vitamin D deficiency were defined as cardiometabolic risk factors. We used standard cut-off values for levels of fasting blood glucose (>100 mg/dL), total cholesterol (≥200 mg/dL), HDL cholesterol (<40 mg/L), LDL cholesterol (≥130 mg/dL), and triglycerides (≥130 mg/dL) to define abnormal values (17). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by using the equation: HOMA-IR = Fasting insulin (μU/mL) x Fasting glucose (mg/dL)/405 (18, 19). Fasting insulin levels above 30 μU/mL was accepted as cut-off levels for hyperinsulinism, and the HOMA-IR cut-off point for the diagnosis of insulin resistance was accepted as 3.16 (18, 19). Seated blood pressure (BP) was measured after the participant had been resting quietly for 10 minutes using the auscultatory method. We used standardized blood pressure tables in which abnormal BP values were defined as >95th percentile (20). Vitamin D deficiency was defined as a 25-OH vit D below 20

ng/mL and vitamin D insufficiency as a 25-OH vit D of 21–29 ng/mL. Vitamin D levels <30 ng/mL were accepted as deficient or insufficient levels in this study (21).

Statistical Analysis

The Statistical Package for the Social Sciences version 21.0 statistical package was used for statistical analyses. Continuous variables were defined as mean±standard deviation (SD) and categorical variables were defined as percentages. The Chi-square test was used to compare categorical variables. In the comparison of continuous variables by groups, the Mann-Whitney U test was used. The relationships between the number of cardiometabolic risk factors and SDS-BMI were evaluated using Spearman's correlation test. To analyze these relationships, we took into consideration subjects who had complete records of all of the variables evaluated in the study except vitamin D. In the assessment of the relationship between cardiometabolic risk factors and SDS-BMI, Pearson's correlation test was used. A series of linear regressions were conducted to determine whether SDS-BMI significantly contributed to the cardiometabolic risk factors including 25-OH vit D level. Sex and age were considered as covariates in the aforementioned models. Logarithmic transformation of insulin was included in looking for correlations and in linear regression analysis because insulin levels did not show normal distribution. The University of California, Los Angeles (UCLA) Institute for Digital Research and Education was used in interpreting logarithmic models (22). A p value of <0.05 was considered statistically significant.

Results

Among 363 adolescents with a BMI at the 85th percentile or higher, 94 (27.5%) were overweight, and 269 (72.5%) were obese. The mean age of the subjects was 14.05±1.75 years and 214 (59%) were girls. The median BMI was 30.34±3.95 kg/m^2 and the median SDS-BMI was 2.38±0.6. The rates of cardiometabolic risk factors are shown in Table 1. The rate of dyslipidemia in obese and overweight adolescents did not differ significantly. Although the rates of hyperinsulinism and insulin resistance were higher, 25-OH D vit levels were low in obese adolescents in comparison with those who were overweight (p<0.001, p=0.001, p=0.038, respectively) (Table 1). When the rates of cardiometabolic risk factors were analyzed separately in terms of sex, the rates of hyperinsulinism and insulin resistance were found significantly higher and 25-OH D vit levels were found significantly lower only among female adolescents who were obese than in female adolescents who were overweight (p<0.001, p<0.001, p=0.024, respectively) (Table 2). Only the rate of hypercholesterolemia was found significantly higher among male adolescents who were obese than in overweight male adolescents (p=0.023) (Table 2).

Table 1. Differences in cardiometabolic risk factors in overweight and obese adolescents

Parameters	Overweight		Obese		p*
	n	%	n	%	
Fasting blood glucose					
High	11	12	39	14.7	0.511
Normal	81	88	226	85.3	
HOMA-IR					
High	46	52.3	188	71.8	**0.001**
Normal	42	47.7	74	28.2	
Hyperinsulinism					
Yes	3	3.4	51	19.3	**<0.001**
No	86	96.6	213	80.7	
Total cholesterol					
High	76	87.4	224	86.5	**0.836**
Normal	**11**	**12.6**	**35**	**13.5**	
Triglyceride					
High	59	67.8	200	75.8	0.144
Normal	28	32.2	64	24.2	
HDL-cholesterol					
Low	71	81.6	208	80.6	0.839
Normal	16	18.4	50	19.4	
LDL-cholesterol					
High	79	89.8	227	88	0.651
Normal	9	10.2	31	12	
High blood pressure					
Yes	15	17.4	73	27.3	0.065
No	71	82.6	194	72.7	
25-OH D vit					
Normal	6	8.2	6	2.2	**0.038**
Low- insufficient	67	91.8	217	97.8	

*Chi-square test. HOMA-IR: Homeostatic model assessment of insulin resistance; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; 25-OH D vit: 25 hydroxy vitamin D

Among 319 of 363 adolescents whose cardiometabolic risk factors were known, 267 (85.7%) had at least one cardiometabolic risk factor, and 52 (14.3%) had no risk factors (Table 3). Using Spearman's correlation analysis, the SDS-BMI had a positive correlation with the number of cardiometabolic risk factors (p<0.001). However, this correlation was weak (r=0.211, p<0.001). No significant difference was found between boys and girls in terms of the number of cardiometabolic risk factors (p=0.433).

Table 2. Differences in cardiometabolic risk factors in overweight and obese adolescents by sex

	Female					Male				
	Overweight		Obese		p*	Overweight		Obese		p*
	n	%	n	%		n	%	n	%	
Fasting blood glucose										
High	7	11.2	22	13.9	0.493	7	21.2	17	14.5	0.867
Normal	55	88.8	126	86.1		26	78.8	100	85.5	
HOMA-IR										
High	28	48.2	30	44.7	**<0.001**	18	60	79	68	0.402
Normal	30	51.8	37	55.3		12	40	37	32	
Hyperinsulinism										
Yes	1	1.7	36	24.5	**<0.001**	2	6.6	15	12.8	0.347
No	58	98.3	111	75.5		28	93.4	102	87.2	
Total cholesterol										
High	48	81.3	130	88.4	0.180	94	84	28	100	**0.023**
Normal	11	18.7	17	11.6		18	16	0	0	
Triglyceride										
High	42	72.4	119	79.8	0.247	17	58.6	81	70.4	0.223
Normal	16	27.6	30	20.1		12	41.4	34	29.6	
HDL-cholesterol										
Low	51	88	122	83.5	0.433	20	70	86	76.8	0.385
Normal	7	12	24	16.5		9	30	26	23.2	
LDL-cholesterol										
High	51	86.4	129	89	0.612	28	96.5	95	86.4	0.135
Normal	8	13.6	16	11		1	3.5	15	13.6	
High blood pressure										
Yes	12	20.6	44	29.5	0.198	3	10.7	29	24.6	0.111
No	46	79.4	105	70.5		25	89.3	89	75.4	
25-OH D vit										
Normal	5	10	3	2.3	**0.024**	1	25	22	19.8	0.999
Low-insufficient	45	90	128	97.7		3	75	89	80.2	

*Chi-square test. HOMA-IR: Homeostatic model assessment of insulin resistance; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; 25-OH D vit: 25 hydroxy vitamin D

In the entire group using Pearson's correlation test, the SDS-BMI had a positive correlation with systolic blood pressure (SBP), diastolic blood pressure (DBP), HOMA-IR, and insulin levels, but had a negative correlation with 25-OH vit D levels ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, and $p=0.003$, respectively). There was a negative correlation between the 25-OH vit D levels and SDS-BMI only in girls ($p=0.023$). Using Pearson's correlation test, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and fasting blood glucose showed no significant correlation with SDS-BMI in the entire group and in both sexes (Table 4).

The results of the linear regression analysis in which sex and age were considered as covariates, the relationship between the cardiometabolic risk factors and SDS-BMI was investigated and is presented in Table 5. An increase of one unit in the SDS-BMI led to an increase of 6.085 mm Hg in SBP, 4.491 mm Hg in DBP, 1.595 points in HOMA-IR, 13% of insulin levels, and a decrease of 2.163 ng/mL in 25-OH vit D levels after adjusting for sex and age (Table 5).

Discussion

In this study, when we analyzed 319 of 363 adolescents, all of whose cardiometabolic risk factors were known, 85.7% had at least one cardiometabolic risk factor, and 14.3% presented no risk factors. These results indicated that overweight and obese adolescents are at increased

Table 3. Distribution of number of cardiometabolic risk factors by sex

Number of cardiometabolic risk factors	Entire group		Female		Male	
	n	%	n	%	n	%
0	52	14.3	35	16.4	17	11.4
1	91	25.1	49	22.9	42	28.2
2	72	19.8	43	20.1	29	19.5
3	61	16.8	34	15.9	27	18.1
4	26	7.2	14	6.5	12	8.1
5	12	3.3	7	3.3	5	3.4
6	3	8	1	0.5	2	1.3
7	2	6	2	0.9	0	0

risk for severe health complications. The results of a study from Germany showed that 70% of overweight or obese children and adolescents had at least one cardiometabolic risk factor (3). In a study from Holland, 80% of 80 children and adolescents with severe obesity were found to have at least one cardiometabolic risk factor (3, 6). Our results are similar to those studies. We also found that as the SDS-BMI increased, the number of the cardiometabolic risk factors increased. In the German study, similar to our findings, children with four or five cardiovascular risk factors were more overweight (high SDS-BMI) than those with less than four cardiovascular risk factors (3). In a study from the United States of America, it was shown that among children and adolescents who were overweight or obese, the greater the severity of obesity, the higher the risks of a low HDL cholesterol levels, high SBP and DBP, and high triglyceride and glycated hemoglobin levels (5). Thus, it could be stated that severe obesity might be associated with significant health problems.

In our study, no relationship was found between the degree of obesity and dyslipidemia in Pearson's correlation analysis, but dyslipidemia was found very frequently; for example, the total cholesterol level was high in over 85% of all adolescents (Table 1), thus, dyslipidemia seems to be an early finding during the cruise of obesity, which needs further investigation.

In our study, it was also found that the risk of hyperinsulinism and insulin resistance increased in both sexes as the degree of obesity increased after controlling for age and sex. Similar results were found in other studies (6, 23). In a study conducted in children and adolescents with obesity, participants with a higher SDS-BMI were found more than five times more likely to have a high HOMA-IR than those with lower SDS-BMI (6). In another study,

Table 4. Relationship between the cardiometabolic risk factors and body mass index SDS (Pearson's correlation test)

	SBP	DBP	Total cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)	Triglyceride (mg/dL)	Fasting blood glucose (mg/dL)	Insulin (μU/mL)	HOMA-IR	25-OH vit D (ng/mL)
SDS-BMI										
Entire group										
r	**0.267****	**0.242****	-0.016	0.003	-0.010	-0.015	-0.007	**0.310****	**0.241****	**-0.174**
p	**<0.001**	**<0.001**	0.761	0.951	0.860	0.777	0.898	**<0.001**	**<0.001**	**0.003**
Female										
r	**0.308****	**0.304****	**0.158***	0.104	0.050	0.014	0.038	**0.336****	**0.253****	**-0.169***
p	**<0.001**	**<0.001**	**0.023**	0.140	0.479	0.842	0.584	**<0.001**	**<0.001**	**0.023**
Male										
r	**0.294****	**0.218***	**0.166***	0.017	0.083	0.063	-0.083	**0.281****	**0.217***	-0.126
p	**<0.001**	**0.008**	**0.050**	0.843	0.327	0.452	0.318	**0.001**	**0.008**	0.178

DBP: Diastolic blood pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein HOMA-IR: Homeostatic model assessment of insulin resistance; SDS-BMI: Body mass index standard deviation; SBP: Systolic blood pressure; 25-OH vit D: 25 hydroxy vitamin D

Table 5. Systolic blood pressure (R^2=0.131), diastolic blood pressure (R^2=0.096), HOMA-IR (R^2=0.063), insulin (R^2=1.264) and 25 hydroxy vitamin D (R^2=0.022) as dependent variables in direct linear regression analysis using age and sex as covariates (1=male, 2=female) and degree of obesity (SDS-BMI) in each model

Variable	SBP		DBP		HOMA-IR		Insulin		25-OH vit D	
	Beta	Sig	Beta	Sig	Beta	Sig	Beta	Sig	Beta	Sig
Sex	-4.29	**<0.001**	-2.96	**0.014**	-0.388	0.347	-0.036	0.146	-0.716	0.498
Age	1.67	**<0.001**	1.076	**0.001**	-0.227	**0.042**	-0.012	0.066	0.094	0.739
SDS-BMI	6.085	**<0.001**	4.491	**<0.001**	1.595	**<0.001**	0.124	**<0.001**	-2.163	**0.008**

DBP: Diastolic blood pressure; HOMA-IR: Homeostatic model assessment of insulin resistance; SBP: Systolic blood pressure; SDS-BMI: Body mass index standard deviation; 25-OH vit D: 25 hydroxy vitamin D; Sig: significance

it was found that among overweight and obese adolescents, mean fasting insulinemia and HOMA-IR values were found to increase significantly from the overweight to the extremely obese girl groups (23).

It is also known that obesity increases the risk of the development of hypertension (24–26). The results of our study demonstrated that the risk of abnormal blood pressure increased as the degree of obesity increased after controlling for age and sex. Similar to our study, other studies showed that the risk of high blood pressure increased as the severity of obesity increased (3, 5, 6).

We found that severity of obesity was inversely related to vitamin D levels after controlling for age and sex. Similar to our results, current evidence suggests that greater obesity leads to lower 25-OH vit D levels, while the opposite relationship is generally not shown (27). There are many possible hypotheses to account for the lower 25-OH vit D concentrations in obese individuals (10, 27–29). The first hypothesis is that adipose tissue absorbs the fat-soluble vitamin D, so measurable vitamin D level is low in obese people (29, 30). Another hypothesis is that obese people have a sedentary lifestyle and are less active physically; therefore, exposure to sunlight and endogenous synthesis of vitamin D decreases among them (29, 31). Also, because of the hepatic steatosis developed in obesity, vitamin D metabolism and 25-OH vit D synthesis might be impaired (29, 32). There is also uncertainty as to what the health consequences of these lower concentrations of 25-OH vit D might be (27, 28, 33). It is emphasized that vitamin D deficiency is associated with type 2 diabetes mellitus, arterial hypertension, heart failure, peripheral arterial disease, acute myocardial infarction, polycystic ovary syndrome, and increased mortality (27, 29). Obesity and vitamin D deficiency are closely related, and both are implicated to be risk factors for cardiometabolic disorders. Accordingly, early intervention targeted toward these modifiable risk factors might prevent future cardiometabolic diseases.

This study has certain methodologic limitations. First, because this is a cross-sectional retrospective study, we could not show causality between the degree of obesity and cardiometabolic risk factors, including 25-OH vit D levels. Second, although we used standard definitions of abnormal values for risk-factor variables, the cross-sectional design did not allow us to examine the effects of these abnormal values on future morbidity or mortality. Lastly, in the multivariate analysis, the adjusted R^2 was low, so only a minor proportion of variability of dependent variable can be explained by the change in independent variables.

In conclusion, our findings show that some cardiometabolic risk factors are related to the degree of obesity, and these findings support the necessity for the determination of the degree of obesity. Whatever the criteria for the determination of obesity severity, an improved estimation of risk that is based on obesity severity could lower the costs of evaluation without resulting in missed diagnoses of coexisting conditions. Children with severe obesity already have increased cardiometabolic risk, which may predict the early onset of serious diseases such as hypertension and diabetes. Although prevention remains the primary goal in the management of obesity, the increasing number of obese subjects confronts healthcare professionals with the complications of obesity. As the end-points of obesity-related co-morbidities will occur by time, appropriate predictors of outcomes after interventions have to be defined. Also, additional research is necessary to determine whether low vitamin D levels might have an impact on the subsequent development of cardiovascular disease during adulthood among adolescents with obesity.

Ethics Committee Approval: The study was conducted in accordance with the principles of the 2008 Declaration of Helsinki. Ethics committee approval was obtained for the study (Faculty Deanship Clinical Research Ethics Committee, Date: 20.06.2016; Number: 29430533-604.01.01-225233).

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