Research Article

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The relation of vitamin D receptor gene polymorphisms with risk of obesity, metabolic syndrome, hepatosteatosis in Turkish children

Vitamin D reseptör gen polimorfizmlerinin Türk çocuklarında obezite, metabolik sendrom ve hepatosteatoz ile ilişkisi

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Abstract

Purpose: The aim of this study was to determine the relation of vitamin D receptor gene (VDR) polymorphisms of TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), FokI (rs10735810) with the risk of obesity, metabolic syndrome and hepatosteatosis in children.

Materials and methods: 130 obese and 130 healthy children of age range between 10-16 years were included in this study. Anthropometric measurements, biochemical evaluations and abdominal USG of all children were done. Obese and healty children were analyzed for the most common polymorphisms of the VDR gene by restriction fragment length polymorphism's technique. The diagnosis of metabolic syndrome was made using the International Diabetes Federation criteria.

Results: Genotypic distribution of BsmI, FokI, and TaqI polymorphism were found statistically different between obese patients and control group, but genotypic distribution of all studied polymorphisms were not found statistically different in obese patients with metabolic syndrome or hepatosteotosis.

Conclusion: BsmI polymorphism (rs1544410) was found to have a significant positive effect on the development of obesity, metabolic syndrome and hepatosteatosis. Children who carry risk factors for childhood obesity could be screened before the development of obesity and associated metabolic complications using the BsmI polymorphism of the VDR gene.

Key words: Obesity, polymorphism, Vitamin D, metabolic syndrome.

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Öz

Amaç: Bu çalışmanın amacı, TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), FokI (rs10735810) gibi Vitamin D reseptör (VDR) polimorfizmlerinin çocuklarda obezite, metabolik sendrom ve hepatosteatoz riski ile ilişkisini belirlemektir.

Gereç ve yöntem: Çalışmaya yaşları 10-16 arasında değişen 130 obez ve 130 sağlıklı çocuk dahil edildi. Tüm çocukların antropometrik ölçümleri, biyokimyasal değerlendirmeleri ve batın USG'leri yapıldı. Obez ve sağlıklı çocuklar, VDR geninin en yaygın polimorfizmlerine restriksiyon fragment uzunluğu polimorfizm yöntemi kullanılarak analiz edildi. Metabolik sendrom tanısı Uluslararası Diyabet Federasyonu kriterleri kullanılarak konuldu.

Bulgular: BsmI, FokI ve TaqI polimorfizminin genotipik dağılımı, obez hastalar ve kontrol grubu arasında istatistiksel olarak farklı bulundu, ancak çalışılan tüm polimorfizmlerin genotipik dağılımı, metabolik sendromlu veya hepatosteotozu olan obez hastalarda istatistiksel olarak farklı bulunmadı.

Sonuç: VDR geni BsmI polimorfizminin (rs1544410) obezite, metabolik sendrom ve hepatosteatoz gelişimine katkısının olduğu bulundu. Obezite gelişim riski taşıyan çocuklarda, obezite ve komplikasyonlar oluşmadan önce tespit etmek için BsmI polimorfizmi tarama amaçlı kullanılabilir.

Anahtar kelimeler: Obezite, polimorfizm, D vitamini, metabolik sendrom.

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Introduction

Obesity is the most common metabolic disorder worldwide and a potential risk factor for many life-threatening preventable diseases. Environmental factors and genetic background may contribute to the development of obesity through an increase in adipocyte number and size. Adipose tissue (AT) is an active endocrine organ which not only takes part in the storage of energy and the regulation of thermogenesis but also known to synthesize and secrete a large variety of anti-inflammatory and pro-inflammatory molecules. These are adipokines, chemokines, and cytokines that enable communication with autocrine, paracrine or endocrine signaling pathways [1].

Vitamin D is a unique fat-soluble vitamin synthesized from 7-dehydrocholesterol by direct contact with sunlight on human skin playing an important role in calcium balance and bone metabolism as well as regulating cell proliferation and differentiation in extra skeletal tissues [2]. Paracrine and autocrine effects of vitamin D occur as a result of binding of active vit D to vitamin D receptor (VDR) that is a member of the nuclear receptor-family in the cell nucleus. VDR mediating the biological functions of vitamin D is found in varying concentrations in nearly all nucleated cells of our body shows that active vitamin D has a direct or indirect effect on the regulation of a large number of genes [3]. The genomic effect of vitamin D through VDR receptors is thought to be effective in the pathogenesis of health and diseases such as cancer, metabolic syndrome, obesity, diabetes, skin diseases, immunity, inflammation, and organ transplantation-related complications [4]. In addition to these genomic effects of Vit D, it is also known to have epigenetic effects by activating signaling pathways, DNA methylation and histone acetylation [5].

Though the association between vit D and obesity is known, whether obesity is a consequence of vit D deficiency or vice versa is not yet known. Nevertheless, the expression of VDR in white and brown adipose tissue and the existence on 3T3-L1 adipocytes was reported. This shows that vit D may be effective in the development of inflammation and insulin resistance, which have a role in the development of obesity-related diseases [6].

The aim of study was to determine the relation of VDR polymorphisms *of TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), FokI (rs10735810)* with obesity, metabolic syndrome and hepatostetosis in children.

Materials and methods

Study Population

A total of 130 obese and 130 healthy control children aged 10-16 years, who were referred to pediatric endocrinology outpatient clinic of the university hospital between January 2015 and June 2015, were evaluated. Exclusion criteria were secondary obesity due to the presence of genetic and/or endocrinological disease or the use of any medication. Tanner criteria were used for pubertal staging. Weight was measured with a balance beam scale with an accuracy of 0.001 kg, and height was measured with a manual height board with an accuracy of 0.1 cm. Body mass index (BMI) was calculated according to the formula body weight (kg) / height squared (m^2). Obesity was defined as BMI ≥ 95th percentile for age and sex according to published standards [7]. The diagnosis of metabolic syndrome was made using the International Diabetes Federation criteria (IDF) [8].

This study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee, and the parents of all children approved the written informed consent at the beginning of the study.

Biochemical assessments

After the overnight fasting, venous blood samples were drawn to assess glucose, insulin, alanine transaminase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C). In all subjects, thyroid function tests were assessed to exclude hypothyroidism. Serum glucose and insulin were used for the calculation of *homeostasis model assessment* (HOMA-IR)=[fasting insulin (mIU/mL)×fasting glucose (mg/dL)/22.5] (mg/dL=mmol/L×18.182).

Imaging of steatosis

Brightness mode ultrasound were performed by using SiemensSonoline G 50 / Italy with 3.5 MHz convex transducers. Degree of hepatic echogenicity scaled by visualization of the

intrahepatic vessels and diaphragm was used to show the presence or absence of steatosis.

Genotyping

DNA samples were obtained from blood leukocytes using a genomic DNA kit according to the manufacturer's instructions (QIAamp DNA Accessory Set, Micro and Min Kits-QIAGEN), and stored at –20 °C until further analysis. VDR *TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), FokI (rs10735810)*, genotyping was conducted by restriction fragment length polymorphism's technique. Four different fragments, which consisted of recognized VDR variants, were produced by fragmenting samples of DNA with the application of restriction enzymes. The produced DNA products were subjected to agarose gel electrophoresis and allele identification and genotyping were done.

Statistical analysis

SPSS (Statistical Packard for Social Sciences) for Windows statistical software version 18.0 was used for all calculations. Data distribution was analyzed using the Kolmogorov-Smirnov test. Anthropometric, biochemical parameters were compared by Student t test. Chi-square test was used to assess categorical variables. A multiple regression model was used to predict the relationship of obesity, MetS, and hepatosteatosis with VDR BsmI polymorphism. In all analyses, a p-value ≤0.05 was considered significant.

Results

A total of 260 children, 130 of whom were obese and 130 of whom were healthy, participated in the study. The mean age of 70 (53.8%) girls and 60 (46.2%) boys (46.2%) of obese children participating in the study was calculated as 13.0±2.25 years. There were 69 (53.1%) girls and 61 (46.9%) boys (46.9%) in the control group with a mean age of 12.9±1.9 years. Of the obese children, 14 (10.8%) were in the prepubertal period, 116 (89.2%) were in the pubertal period, 8 (6.2%) of the children in the control group were in the prepubertal period and 122 (93.8%) were in the pubertal period. There was no difference between the two groups by means of age, gender, and puberty. In the comparison of anthropometric and biochemical findings of obese and control group children, no differences were found between height, blood glucose level and AST level, but all the other parameters were found to be statistically different between the two groups (Table 1, 2). Liver USG could not be performed in four of the obese children participated in the study because they did not come to their appointment. Fatty liver disease was diagnosed by B-Mod USG in 78 (61.90%) obese children and metabolic syndrome was diagnosed in 20 (15.38%) obese children according to IDF criteria. BMI and waist circumference measurement (30.72±4.63 kg/m^2 / 100.12±12.33 cm) in obese children with hepatic steatosis were found to be statistically significantly higher than those without hepatic steatosis (29.01±4.22 kg/m^2 / 94.64±12.61 cm) respectively (p=0.032, p=0.017).

Table 1. Anthropometric characteristics of children

	Obese children (n:130)	Healty control (n:130)	*p*
Sex (F/M) (n, %)	70/60 (53.8/46.2)	69/61 (53.1/46.9)	0.901
Age (years)	13.08±2.25	12.93±1.91	0.514
Weight (kg)	76.27±19.59	46.85±9.04	<0.001*
Weight SDS	2.47±1.03	-0.42±0.78	<0.001*
Height (cm)	158.23±12.70	155.94±11.18	0.222
Height SDS	0.24±1.16	-0.09±0.87	0.026*
BMI (kg/m^2)	30.04±4.48	18.93±2.13	<0.001*
Bmi SDS	2.41±0.62	-0.44±0.79	<0.001*
Waist circumference (cm)	98.03±12.58	69.86±6.97	<0.001*
Systolic blood pressure (SBP) (mmHg)	118.42±12.26	107.73±9.46	<0.001*
Diastolic blood pressure (DBP) (mmHg)	75.96±9.04	68.35±6.97	<0.001*
Prepubertal/pubertal) (n, %)	14/116 (10.8/89.2)	8/122 (6.2/93.8)	0.181

F/M; female/male, SDS; standart deviation score, BMI; body mass index, * *p* values <0.05 are statistically significant

Table 2. Metabolic variables of obese patients and control group

	Obese children (n:130)	Healthy conrol (n:130)	*p*
Glucose (mg/dl)	90.97±7.05	90.63±8.76	0.966
Insulin (uIU/mL)	20.87±10.48	9.05±2.78	<0.001*
HOMA-IR	4.72±2.51	2.02±0.63	<0.001*
AST (IU/L)	20.00±5.11	19.35±5.45	0.340
ALT (IU/L)	19.83±11.12	13.21±4.97	<0.001*
Trigliserid (mg/dl)	105.50±50.29	85.03±41.36	<0.001*
Total Kolesterol (mg/dl)	157.18±29.83	139.06±27.69	0.002*
LDL (mg/dl)	87.58±25.16	70.86±18.30	<0.001*
HDL (mg/dl)	48.55±11.19	56.90±12.93	<0.001*

HDL: high density lipoprotein, LDL: low density lipoprotein, ALT;alanine transaminase, AST;aspartate aminotransferase, HOMA-IR: homeostasis model assessment for insulin resistance, *p* values <0.05 are statistically significan

Genotypic distribution of all single nucleotide polymorphisms (SNP) is presented in Table 3. Genotypic distribution of BsmI polymorphism, FokI polymorphism, TaqI polymorphism were found statistically different between obese patients and control group. But genotypic distribution of all studied SNPs were not found statistically different in obese patients with metabolic syndrome or hepatosteotosis (respectively $p>0.286$, $p>0.341$, $p>0.563$, $p>0.401$).

All studied SNPs were evaluated by using the Hardy-Weinberg equilibrium. Only BsmI polymorphism is within the equilibrium ($p\geq0.05$). In contrast, FokI polymorphism, TaqI polymorphism, and ApaI polymorphism) showed a deviation from the Hardy-Weinberg equilibrium, so we didn't use them for further analysis in the study. BsmI polymorphism of VDR showed that the heterozygous 'Bb' genotype is predominant in the distribution of obese patients (79.2%), and the 'bb' genotype is predominant in the control group (92.3%). The frequency of allele 'B' and 'b' was 0.311 and 0.689 respectively in the study groups for BsmI polymorphism.

Regression analysis showed BsmI polymorphism was found to have significant positive effect on the development of obesity, metabolic syndrome and hepatosteotosis (Table 4).

Table 3. Vitamin D receptor gene BsmI, ApaI, FokI, TaqI, polymorphisms in children with obesity and the control group

Genotypes	Obese children (n:130)	Healthy children (n:130)	*p*
BsmI			
BB	18 (13.8%)	10 (7.7%)	<0.001*
Bb	103 (79.2%)	0 (0%)	
bb	9 (7%)	120 (92.3%)	
FokI			
FF	94 (72.3%)	60 (46.1%)	<0.001*
Ff	34 (26.1%)	64 (49.2%)	
ff	2 (1.6%)	6 (4.7%)	
ApaI			
AA	43 (33.0%)	48 (36.9%)	0.087
Aa	64 (49.2%)	71 (54.6%)	
aa	23 (17.8%)	11 (8.5%)	
TaqI			
TT	43 (33.0%)	1 (0.7%)	<0.001*
Tt	65 (50.0%)	114 (87.7%)	
tt	22 (17.0%)	15 (11.6%)	

p values <0.05 are statistically significant

Table 4. Association of VDR gene polymorphism with obesity, hepatosteotosis, metabolic syndrome in Turkish children at regression analysis

	Unstandardized Coefficients		Standardized Coefficients	R Square		
Model	**B**	**Std. Error**	**Beta**		**95.0%CI for B**	***p***
Bsm1[a]	0.495	0.048	0.539	0.29	0.400-0.590	0.000
Bsm1[b]	0.137	0.032	0.258	0.06	0.074-0.200	0.000
Bsm1[c]	0.854	0.032	0.854	0.72	0.79-0.918	0.000

a. Dependent Variable: Hepatosteotosis
b. Dependent Variable: Metabolic syndrome
c. Dependent Variable: Obesity

The 'BB' genotype showed a 36.92 times increased risk of obesity (p=0.000, (OR=36.92 (95%CI 5.48-248.77)), a 27.82 times increased risk of MS (p=0.003, (OR=27.82 (95%CI 3.1-249.23)), and a 6.10 times increased risk of hepatostetosis (p=0.002; (OR=6.1 (95%CI 1.93-19.25)). The 'Bb' genotype showed a 20.13 times increased risk of MS (p=0.003, (OR=20.13 (95%CI 2.60-155.89)) and 32.36 times increased risk of hepatostetosis (p=0.002; (OR=6.1 (95%CI 1.93-19.25)) in comparison to individuals who are homozygous for ''bb'' genotype.

Discussion

In this study, we investigated the relationship of vitamin D receptor ApaI, BsmI, TaqI and FokI gene polymorphisms with childhood obesity, metabolic syndrome and fatty liver disease, and only BsmI gene polymorphism was found to be related with obesity, fatty liver and metabolic syndrome. Those with 'BB' and 'Bb' genotypes of VDR BsmI were found to be significantly associated with an increased risk of having obesity, MS, and hepatosteatosis compared to the 'bb' genotype. To our knowledge, this is the first study to report that VDR polymorphisms are associated with obesity, hepatostetosis, and MS in Turkish children. The adipose tissue (AT) is known as an active endocrine organ playing an important role in metabolic, hormonal and immunological processes. AT contains a lot of cell types such as adipocytes, immune cells, endothelial cells, smooth muscle cells and fibroblasts. The degree of obesity determines secretory activity of adipose tissue by changing number of cell types, phenotype and distribution. A hypoxic environment, adipose tissue fibrosis, and macrophage infiltration of AT caused by obesity may trigger an inflammatory response and the production of inflammatory mediators [9]. This immune dysregulation in adipose tissue eventually results in chronic low-grade systemic inflammation that is accused of the pathogenesis of obesity related-disease processes [10]. Obesity induced adipose tissue remodeling explains how an inflammatory response is initiated, nevertheless most of the inflammatory triggers are still unknown. It was shown that obesity was associated with low serum 25 (OH) D levels as well as related to VDR in many cross-sectional previous studies [11-14]. Vit D controls the inflammatory response through the VDR located on adipocytes and macrophages in adipose tissue even though evidence to support a causal link is still inadequate and the contribution to the pathophysiological mechanism is not very clear [15, 16].

The present study showed that 'BB' and 'Bb' genotypes of BsmI gene polymorphism were associated with obesity, metabolic syndrome, hepatosteatosis. Of the obese patients, 72% of patients with obesity, 29% with hepatosteatosis, and 6% with metabolic syndrome could be explained by having the BsmI polymorphism alone.

Minor allele carriers of the SNP BsmI (rs1544410) were at higher risk of an increased BMI, and BsmI gene polymorphism was more frequent in obese individuals of Arabian people showed by the previous studies [17, 18]. Contrary to the study of Sharife et al. [17], individuals carrying the major allele (G) of the Bsm I gene were at risk of obesity in a study conducted in North China [19]. Wang et al. [20] genotyped Cdx2, BsmI, TaqI, ApaI, and FokI in the VDR gene of 106 overweight/obese and 86 healthy control Chinese children to search association of VDR with MetS. They

found significantly increased risk of MetS with the FokI AA genotype, and ApaI AA genotype was correlated with overweight/obesity [20]. Cobayashi et al. [21] studied the same gene polymorphisms in the VDR gene of Brazilian children as did Wang et al. [20] and they found only VDR BsmI gene polymorphism was associated with metabolic parameters [21]. These reported contradictory results between studies may be due to the diversity of genetic backgrounds even in the same population, sample size, age range, environmental factors, and methodology.

How VDR polymorphisms are related to the disease was studied by many investigators and BsmI polymorphism of the VDR gene was shown to affect the target cells by changing the VDR length and configuration, altering the intronic regulatory elements, changing mRNA stability, or disrupting mRNA transcription splice sites [22]

The major limitations of the current study are as follows; first, the number of samples size may not be sufficient to generalize the results to the population. Second, we did not determine the serum 25 (OH) D level. Third, we didn't include healty control and obese patients under ten years old. Fourt and last, all VDR polymorphisms were not investigated.

In conclusion, this study showed that BsmI polymorphisms of the VDR gene were strong risk factors for obesity, metabolic syndrome and hepatosteatosis respectively. Children who carry risk factors for childhood obesity such as birthweight abnormality, paternal obesity, gestational diabetes, sleep disturbances, and sedentary lifestyle could be screened before the development of obesity and associated metabolic complications using BsmI polymorphisms of the VDR gene and this information might be used to identify and timely management of children at risk of obesity. To validate the results, further studies with larger multiethnic cohorts would be required.

Conflict of interest: No conflict of interest was declared by the authors.

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Author contributions

B.O. and E.B. designed the study, performed the data collection, wrote the draft, and created the tables for the manuscript. G.O.C. and K.A. designed the study, performed data collection and analysis, and revised the article. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.