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Vitamin D receptor gene polymorphism in Polish patients with morbid obesity**

Polimorfizm genu receptora witaminy D u polskich pacjentów z otyłością olbrzymią

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Key words

gene, obesity, polymorphism, vitamin D, vitamin D receptor

Słowa kluczowe

gen, otyłość, polimorfizm, witamina D, receptor witaminy D

Summary

Introduction. Obesity has important medical, psychosocial and economic consequences which are greater than those of many other chronic disorders. Active form of vitamin D, $1,25(OH)_2D$ exerts its actions through binding to the vitamin D receptor (VDR). Some data suggest a role of vitamin D and VDR polymorphism in obesity and its metabolic complications.

Aim. Our objective was a preliminary evaluation the association of *VDR* gene FokI and BsmI polymorphism and body mass index (BMI), inflammatory parameters (C-reactive protein – CRP, erythrocyte sedimentation rate – ESR), hypertension, dyslipidemia and hyperglycemia in a morbidly obese Polish patients.

Material and methods. The study involved 152 morbidly obese patients (BMI $\geq$ 40 kg/m^2) and 100 healthy controls. DNA was extracted from peripheral blood. Genotyping was performed by real-time PCR using LightSNiP tests with SimpleProbe probes. Melting curve analysis of PCR amplicons enabled identification FokI and BsmI genotypes.

Results. There were no significant differences between morbidly obese patients and control subjects in the distribution of FokI and BsmI genotypes or alleles. No association between VDR FokI and BsmI polymorphism was observed with the BMI, CRP, ESR, hypertension, dyslipidemia and hyperglycemia.

Conclusions. Based on our results, it can be concluded that FokI and BsmI polymorphism is not associated with the BMI, inflammatory parameters and the frequency of hypertension, dyslipidemia and hyperglycemia in Polish patients with morbid obesity. Our observations should be considered as preliminary. Further studies on larger cohorts of individuals are thus urgently needed to shed more light on the value of assaying the VDR polymorphism in obesity.

Streszczenie

Wstęp. Otyłość niesie za sobą poważne konsekwencje medyczne, psychospołeczne i ekonomiczne, przewyższając inne przewlekłe schorzenia. Aktywna forma witaminy D – $1,25(OH)_2D$, działa za pośrednictwem receptora VDR. Niektóre badania sugerują, iż witamina D i polimorfizm jej receptora mogą uczestniczyć w rozwoju otyłości i jej powikłań metabolicznych.

Cel pracy. Celem niniejszej pracy była wstępna ocena związku polimorfizmu FokI i BsmI genu *VDR* z indeksem masy ciała (ang. *body mass index* – BMI), parametrami stanu zapalnego: CRP (białko C-reaktywne, ang. *C-reactive protein*), OB (odczyn Biernackiego), występowaniem nadciśnienia, dyslipidemii i hiperglikemii u pacjentów z otyłością olbrzymią.

Materiał i metody. W badaniu wzięło udział 152 pacjentów z otyłością olbrzymią (BMI $\geq$ 40 kg/m^2) oraz 100 ochotników z prawidłową masą ciała. DNA zostało wyizolowane z pełnej krwi obwodowej. Genotypowanie wykonano metodą łańcuchowej reakcji polimerazy w czasie rzeczywistym (real-time PCR) z wykorzystaniem testów LightSNiP i sond SimpleProbe. Analiza temperatury topnienia amplikonów umożliwiła identyfikację genotypów FokI i BsmI genu *VDR*.

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Wyniki. Nie wykazano istotnych różnic w częstości występowania genotypów i alleli FokI i BsmI w grupie chorych z otyłością olbrzymią i grupie kontrolnej. W badaniu nie stwierdzono zależności polimorfizmu FokI, BsmI i BMI, CRP, OB oraz częstości występowania nadciśnienia, dyslipidemii i hiperglikemii.

Wnioski. Na podstawie uzyskanych wyników można wnioskować, iż polimorfizm FokI i BsmI genu *VDR* nie ma związku z indeksem masy ciała, parametrami stanu zapalnego oraz częstością występowania nadciśnienia, dyslipidemii i hiperglikemii u polskich pacjentów z otyłością olbrzymią. Nasze obserwacje należy traktować jako wstępne. Dalsze badania na większych grupach osób są konieczne, aby rzucić więcej światła na potrzebę oznaczania polimorfizmu VDR w przypadku otyłości.

INTRODUCTION

Obesity is one of the most serious public health problem of the 21st century (1). The World Health Organization defines obesity as a body mass index (BMI) of 30 kg/m^2 or more. Morbid obesity is defined as a BMI of 40 kg/m^2 (2, 3). **Obesity is associated with an increased risk of several diseases (i.e. coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes, cholelithiasis, pulmonary embolism, sleep apnea, psychiatric illness and malignancy: breast, endometrial, prostate and colon)** (1, 2).

Vitamin D plays an important role in skeletal metabolism, but has also been shown to be a potential key hormone in immune homeostasis, glucose and lipids metabolism and other non-calcemic actions (4). Active form of vitamin D – calcytriol (1,25(OH)$_2$D) exerts its actions in a variety of cell types through binding to the nuclear vitamin D receptor (VDR) which functions as a ligand-dependent transcriptional factor of many genes (5-11). VDR and 1α-hydroxylase (an enzyme, which catalyses conversion of 25(OH)D to 1,25(OH)$_2$D) is expressed in more than 40 cell types, such as bone, brain, colon, prostate, immune cells, adipocytes, pancreas, and many others (12-16). *VDR* is a product of VDR gene locus (on chr12q13.1). Several VDR polymorphisms have been found: including FokI, ApaI, BsmI, TaqI, EcoRV, Tru91, Cdx2. The most frequently studied is FokI and BsmI. These are single nucleotide polymorphisms (SNiPs). FokI (rs2228570, T/C) polymorphism is located in the second start codon (ATG) in exon 2. When the C (mutant) allele is present, an alternative start site is used, leading to the expression of a shorter VDR protein (424 aa), which demonstrates a greater transcriptional activity as a consequence of enhanced binding to transcription factor II B. The T (wild-type) allele leads to expression of a longer VDR protein (427 aa). BsmI (rs1544410, G/A) polymorphism is located in intron 8 and affects the level of VDR gene transcription, transcript stability, and posttranscriptional modifications (17-22). *VDR* gene polymorphism and vitamin D deficiency may cause bone diseases (rickets, osteomalacia, osteoporosis) but also may be a risk factor for other chronic disorders, such as type 2 diabetes, cardiovascular problems, autoimmune diseases (systemic lupus erythematosus, inflammatory bowel disease, scleroderma mellitus, type 1 diabetes, asthma, allergies), psychiatric illness and many others (5, 11, 14, 22-25).

The role of vitamin D and vitamin D receptor in adipocyte metabolism and obesity is not fully explained. VDR is expressed in preadipocytes and may contribute to the action of vitamin D. 1,25(OH)$_2$D via VDR inhibits preadipocytes differentiation *in vitro* and in animal models (26-28). Moreover vitamin D and VDR is important in the mechanism of insulin release and in the maintenance of glucose tolerance. Vitamin D deficiency and VDR polymorphism may lead to impaired insulin secretion, insulin resistance and may contribute to excessive adipose tissue deposition (29). Moreover vitamin D via its receptor affects hepatic lipid metabolism, promotes intestinal calcium absorption, and calcium may bind to fatty acids to form insoluble complexes that inhibit lipid absorption. Thus, vitamin D deficiency and VDR polymorphism may lead to abnormal processing of lipids due to alterations in calcium availability (30, 31).

Vitamin D via VDR modulates cytokine production, which may have an impact on the inflammatory activity of adipose tissue (32, 33).

Variations at the *VDR* gene are linked with susceptibility to many disorders. Some literature suggests that vitamin D deficiency and *VDR* polymorphism may contribute to the development of overweight and obesity (34-37).

AIM

Obesity has became a global epidemic, therefore there is increasing interest in the role of factors that possibly contribute to its development. We conducted this study to investigate the possible association of vitamin D receptor gene FokI and BsmI polymorphism with the body mass index, inflammatory parameters and frequency of hypertension, dyslipidemia, hyperglycemia in a group of morbidly obese Polish patients.

MATERIAL AND METHODS

Subjects

Participants provide their written informed consent to participate in this study. The ethics committee of Medical Centre of Postgraduate Education, Warsaw, Poland approved this procedure and the study (agreement No. 49/PW/2011), 02.03.2011.

We studied a group of 152 morbidly obese Polish patients (BMI $\geq$ 40 kg/m^2). All patients (100 women, 52 men) were admitted to the Department of Family Medicine, Internal Medicine and Metabolic Bone Diseases, Prof. W. Orlowski Hospital, Warsaw for medical tests before bariatric surgery. The control group consisted 100 anonymous healthy

blood donors with normal weight (BMI 19-24 kg/m^2). Measurement of growth was taken by PROSTAND stadiometer Seca 210. Weight was measured with a balance beam scale. ESR and CRP were measured at the prof. W Orlowski Hospital laboratory. The characteristics of the patients and controls is shown in table 1.

Table 1. Characteristics of morbidly obese patients and controls. Data are expressed as minimum – maximum, means ± standard deviation and percentage.

	Patients	Controls
Subjects	152	100
Gender (male/female)	100/52	63/37
Age (years)	18-76 (42.93 ± 11.20)	18-61 (40.28 ± 9.20)
BMI (kg/m^2)	41-75 (45.63 ± 10.0)	19-24 (21.25 ± 1.82)
CRP (mg/l)	0.5-144 (11.71 ± 17.63)	NM
ESR (mm/1h)	3-80 (20.86 ± 14.08)	NM
Treatment for hypertension [n (%)]	129 (85)	No
Treatment for dyslipidemia [n (%)]	94 (62)	No
Treatment for hyperglycemia [n (%)]	146 (96)	No

BMI – body mass index; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; NM – not measured

DNA isolation and genotyping

Genomic DNA was extracted from peripheral blood samples by standard procedures using the Blood Mini kit (A&A Biotechnology, Poland). VDR FokI (rs2228570, T/C) and BsmI (rs1544410, G/A) genotyping was performed by LightCycler real-time PCR (Roche, Germany) using commercial LightSNiP (SimpleProbe) assays from TIB-MolBiol (Germany) according to the manufacturer's recommendations. Melting curve analysis of PCR amplicons enabled identification individual FokI and BsmI genotypes of vitamin D receptor gene. The genotypes were classified as homozygote major allele (TT for FokI, GG for BsmI), heterozygote (TC, GA) and homozygote minor allele (CC for FokI, AA for BsmI).

Statistical analyses

Statistical analyses was performed using Statistica 10.0 (StatSoft Inc). To compare the frequency of genotypes and alleles of VDR FokI and BsmI polymorphisms in patients with morbid obesity and control group the Freeman-Halton extension of Fisher's exact test for contingency table was used. Correlation analysis of FokI and BsmI genotypes with body mass index, C-reactive protein level, erythrocyte sedimentation rate, treatment for hypertension, dyslipidemia and hyperglycemia was performed using Spearman's Rank Correlation Test. Hardy-Weinberg equilibrium (HWE) was determined by Pearson's χ^2 goodness-of-fit test. Differences were considered statistically significant at a p value < 0.05.

RESULTS

FokI and BsmI genotype and allelic frequencies for patients and controls are presented in tables 2 and 3. The distribution of FokI and BsmI genotypes was consistent with Hardy-Weinberg equilibrium in the two groups. The VDR FokI genotype frequencies of TT, TC and CC was respectively 15, 57 and 28% in obese patients and 18, 53 and 29% in the control group. The VDR BsmI genotype frequencies of GG, GA, AA was respectively 41, 49, 10% in patnets and 41, 42 and 17% in controls. There were no significant differences between morbidly obese patients and control subjects in the distribution of FokI and BsmI genotypes or alleles.

Table 2. VDR FokI genotype and allele frequencies of morbidly obese patients and control group.

	FokI genotypes			Alleles	
	TT (wt)	TC	CC (mt)	T	C
Patients n (%)	23 (15)	86 (57)	43 (28)	132 (43)	172 (57)
Controls n (%)	18 (18)	53 (53)	29 (29)	89 (44)	111 (56)
p value	0.795			0.855	

wt – wild-type; mt – mutant

Table 3. VDR BsmI genotype and allele frequencies of morbidly obese patients and control group.

	BsmI genotypes			Alleles	
	GG (wt)	GA	AA (mt)	G	A
Patients n (%)	62 (41)	75 (49)	15 (10)	199 (65)	105 (35)
Controls n (%)	41 (41)	42 (42)	17 (17)	124 (62)	76 (38)
p value	0.210			0.449	

wt – wild-type; mt – mutant

Various parameters (BMI, CRP, ESR, hypertension, dyslipidemia, hyperglycemia) were compared among morbidly obese patients being carriers of the different FokI and BsmI genotypes.

We have observed no association between FokI genotypes and BMI, inflammatory parameters (CRP, ESR), hypertension, dyslipidemia, hyperglycemia. Moreover no significant differences in these trials have been observed for BsmI genotypes in this group of patients (tab. 4).

DISCUSSION

Our study included patients with morbid obesity (BMI $\geq$ 40 kg/m^2) and to our knowledge is the first which evaluates the association of FokI and BsmI polymorphism and body mass index, inflammatory parameters (CRP, ESR), hypertension, dyslipidemia, hyperglycemia in such patients.

There were no difference in the FokI and BsmI genotypes distribution in controls and obese patients which is in line with previous studies (25, 37).

The FokI polymorphism (T/C transition) is located in the second start codon (ATG) in exon 2 and results in a shorter protein with increased biological activi-

Table 4. Spearman's rank correlation calculated between FokI and BsmI genotypes and BMI, CRP, ESR, hypertension, dyslipidemia, hyperglycemia.

	BMI (kg/m^2)	CRP (mg/l)	ESR (mm/1 h)	Hypertension	Dyslipidemia	Hyperglycemia
FokI genotypes*	0.520	0.897	0.295	0.429	0.834	0.093
BsmI genotypes**	0.160	0.981	0.325	0.876	0.454	0.734

*ranks: 0 – TT genotype; 1 – TC genotype; 2 – CC genotype
**ranks: 0 – GG genotype; 1 – GA genotype; 2 – AA genotype

ty (17, 22). We have observed no association for FokI with BMI, CRP and ESR in morbidly obese patients. The BsmI polymorphism (G/A transition) is located in intron 8 and affects the level of *VDR* gene transcription, transcript stability, and posttranscriptional modifications (17, 22). We have shown that BsmI in not associated with the BMI, CRP and ESR in morbidly obese patients as well as FokI. Moreover our data suggest that VDR is not a major gene for hypertension, lipid metabolism disorders and hyperglycemia in this group of patients.

There is a small amount of data concerning the role of vitamin D and its receptor gene polymorphism in the development of obesity and its metabolic consequences. These few studies present conflicting results, which may be explained in part by the differences in sample sizes, ethnic background, statistical methods and environmental factors.

In 2001, Ye et al. analyzed the association between VDR polymorphism and obesity in French patients with type two diabetes. The study showed no difference in the genotypes distribution in the study group compared to the controls. For BsmI polymorphism there was demonstrated that the presence of homozygous GG favors higher values of body mass index. For FokI polymorphism any significant associations were observed (25). In 2006 Filus et al. examined the association between BsmI and FokI polymorphisms and parameters describing metabolic syndrome in randomly selected Polish men. It has been shown that the presence of homozygous AA of BsmI polymorphism correlates with higher values of BMI and waist circumference. Moreover FokI seems to influence insulin sensitivity and cholesterol levels (35). Similar study was performed in 2013 by Schuch et al. in Brazilian population (36). This study suggest that FokI and BsmI polymorphisms may influence insulin secretion, insulin resistance and serum HDL-cholesterol. In 2011 Ochs-Balcom et al. observed no association for FokI polymorphism with BMI, waist circumference and abdominal height in healthy white American women (37). In 2004 Grundberg et al. demonstrated a correlation of BsmI polymorphism and fat mass and body weight in premenopausal healthy Swedish women (38).

Due to different results of studies on the role of *VDR* FokI and BsmI polymorphism in obesity and its complications, mechanisms behind the genotype/phenotype associations observed for these single nucleotide polymorphisms are still unclear.

CONCLUSIONS

Evidence from our study suggests that VDR FokI and BsmI polymorphism is not related to body mass index, c-reactive protein level and ESR parameter in morbidly obese Polish patients. Moreover our data suggest that VDR is not a major gene for hypertension, lipid metabolism disorders and hyperglycemia in this group of patients.

We admit that the main limitation of this work is relatively small number of patients and controls thus our observations should be considered as preliminary. Further studies on larger cohorts of individuals are thus urgently needed to shed more light on the value of assaying the VDR polymorphism in obesity.

Assessment of these associations will provide greater insight into potentially modifiable risk factors for metabolic syndrome and cardiovascular disease in these high-risk patients.

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