Original article

Association of *VDR Bsm*I gene polymorphism, bone turnover markers and bone mineral density in severe postmenopausal osteoporosis

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Abstract

Currently there is no clear answer whether specific vitamin D receptor gene genotype is associated with lower bone mineral density and higher fracture risk.

The aim of this study was to analyze the associations of vitamin D receptor gene *Bsm*I polymorphisms with bone turnover markers and bone mineral density in postmenopausal women with severe osteoporosis.

Patients and methods. Vitamin D, parathyroid hormone (PTH), bone turnover markers were measured by electrochemical luminescence immunoassay, polymorphism of *VDR* gene (*Bsm*I) was determined using polymerase chain reaction (PCR) analysis. Bone mineral density was measured by the dual-energy X-ray absorptiometry (iDXA, GE Lunar). Differences between groups were determined using ANOVA test. Subgroup corelation analysis was also conducted.

Results. In total, 73 postmenopausal women were included in this study - 28 patients with severe postmenopausal osteoporosis and 45 control persons. It was not found the significant difference of *VDR Bsm*I genotypes between patients and controls. There were no statistically significant correlations between lumbar spine and total hip BMD and biochemical bone markers in bb or *Bb* genotypes either in women with severe osteoporosis or in control women. In patients with severe postmenopausal osteoporosis, the lumbar spine BMD was significantly higher in the *BB* genotype bearers as compared to the *bb* and *Bb* genotype bearers. In patients with severe osteoporosis bearing *VDR Bsm*I *bb* genotype, the vitamin D concentration was negatively related to PTH and positively related to femoral neck BMD; PINP was positively related to s-CTX-I.

Conclusions. The findings of this study suggest that *VDR Bsm*I gene polymorphism has weak non-significant association with BMD level and severe postmenopausal osteoporosis and needs to be further analyzed. In patients with severe postmenopausal osteoporosis, the lumbar spine BMD was significantly higher in the *BB* genotype bearers as compared to the *bb* and *Bb* genotype bearers.

Key words:

vitamin D receptor gene, polymorphism, bone turnover markers, bone mineral density, severe postmenopausal osteoporosis

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Introduction

Osteoporosis is a common disease characterized by compromised bone strength predisposing a person to an

increased risk of osteoporotic fracture which leads to significant morbidity, mortality, and high social and economical burden [1]. Bone mineral density (BMD), the major determinant of bone strength, is a complex trait, resulting from the interplay of genetic and acquired influences, such as life style, hormonal, and nutritional factors [2].

Vitamin D status is a main nutritional determinant of bone health and BMD. Vitamin D inadequacy is associated with higher risk for myopathy, falls, secondary hyperparathyroidism, increased bone turnover, reduced BMD and increased fractures risk [3]. Vitamin D as a part of endocrine system has pleiotropic effect on immune system modulation, regulation of skeletal metabolism and cellular proliferation, and differentiation.

So far, extensive efforts have been made to identify genes predisposing to osteoporosis. Twin and family studies suggest that up to 85% of the variance in BMD could be genetically determined [4, 5]. Other important factors are physical activity and hormonal, and nutritional influences. Over 100 candidate genes associated with bone mineral density and with the risk of osteoporosis have already been identified [6–10]. These are important in the peak bone mass attained and can impact bone metabolism.

Vitamin D receptor (*VDR*) gene is a nuclear transcription factor, that mediates the action of 1,25(OH)2D3, thus affecting calcium absorption, bone remodeling and mineralization rate [11]. The sequence of *VDR* gene was revealed to be polymorphic in different individuals. It is located on the long arm of 12 chromosome (3q11 locus), consists of 11 exons, 2–9 of which are actively transcribed. Since the pioneering work of N.A. Morrison et al. in 1994, who demonstrated the association of the 3′ region *VDR* gene polymorphisms (*Bsm*I, *Apa*I, *Taq*I were identified) with BMD [12], numerous subsequent papers have been published on that topic. Their results have been inconclusive; still there is no clear answer whether specific *VDR* genotype is associated with lower BMD and higher fracture risk [12–15].

The aim of this study was to analyze the association of vitamin D receptor gene *Bsm*I polymorphism with bone turnover markers and bone mineral density in severe postmenopausal osteoporosis.

Material and methods

Study sample

This was a case-control study, which was conducted in National Osteoporosis Center (Vilnius, Lithuania). All participants were Caucasian, community dwelling and ambulatory postmenopausal women. The inclusion criteria were: postmenopausal status, clinical diagnosis of osteoporosis and fragility fracture at hip or spine, confirmed by radiological examination. Exclusion criteria were conditions known to affect bone and mineral metabolism (Paget's disease, osteogenesis imperfecta, rheumatoid arthritis, etc.) or taking medications which may change the bone metabolism (glucocorticosteroids), vitamin D supplements. Subjects who have sustained bone fracture during the last 12 months were also excluded from study. All genotype groups obeyed the Hardy-Weinberg equilibrium.

The local ethics committee has approved the study protocol. Written informed consent was obtained from all participants. The data of medical history, fracture history were obtained, and physical examination was performed.

Biochemical measurements

Venous blood samples were taken after fasting for 12 hours, between 8 and 11 hours into serum vials with an isolating gel. After the blood had clotted at room temperature not more than one hour after the collection the serum samples were centrifuged at room temperature with Labofuge centrifuge (1500 rev/min, for 15 min). After thawing, blood samples were immediately examined for the vitamin D and PTH. For the analysis of bone turnover markers (BTM), the serum samples were stored at –20°C immediately after the separation till examination, but no more than a week. Serum 25-hydroxyvitamin D (25(OH) D), PTH, bone resorption marker serum C-terminal cross-linking telopeptide of type I collagen (s-CTX-I) and bone formation marker procollagen type I N propeptide (PINP) were measured by fully automated electrochemical luminescence immunoassay method (Cobas E411, Roche Diagnostic) using the original reagents, and in accordance with the manufacturer's instructions, regular calibration and quality control applied on a daily basis.

Determination of VDR genotype

For genetic analyses venous blood sample was taken from cubital vein using Vacutainer system (Beckton-Dickinson, Franklin Lakes, NJ, USA). Deoxyribonucleic acid (DNA) was isolated from bloodspots dried on special NucleoSafe cards (Macherey-Nagel, Germany) using standard proteinase K digestion, phenol-chloroform extraction and ethanol precipitation [16]. The DNA solution was extracted with a phenol chloroform isoamyl alcohol mixture to remove protein contaminants, and then precipitated with 100% ethanol. The DNA was pelleted after the pre-

cipitation step, washed with 70% ethanol to remove salts and small organic molecules, and resuspended in buffer at a concentration suitable for further investigation.

Polymorphism of *VDR* gene (*Bsm*I) was determined using polymerase chain reaction (PCR) analysis using specially designed primers. Polymorphic sites in *VDR* (*Bsm*I *B/b*, rs1544410) were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. PCR amplifications of the related regions were carried out in 20 µl volumes of reaction mixtures containing 2 × PCR-buffer (with 3 mM MgCl2), 200 µM of each dNTP, 0,5 µM of each set of specific primers, 1 unit of Tornado-Taq DNA polymerase (Primetech, Belarus) and 20–50 ng of DNA sample. All PCR reactions were run at 95° C for 15 min followed by 30 cycles of 99°C for 1 s, 62°C for 10 s and extension at 72°C for 20 s. The final extension was at 72°C for 2 min were performed in an automated thermal cycler (Applied Biosystems 2720, USA). The amplified products were analyzed by electrophoresis on 8% polyacrylamide gel. *Bsm*I genotypes were analyzed by *Bsm*I (37°C) restriction enzyme digestion (Fermentas), respectively. The *B* allele (191 bp) remained as a single 490 bp band, the *b* allele (115 and 76 bp) alleles were observed as 2 bands. All of the digestion products were analyzed by electrophoresis on 8% polyacrylamide gel.

Bone mineral density

Bone mineral density (g/cm^2) of the lumbar spine (L_1–L_4), total hip and femoral neck was measured by the dual-energy X-ray absorptiometry (iDXA; GE Lunar, USA). Standardized procedures for participants positioning and scan analysis were used by certified operator.

Statistical analysis

Characteristics of the group variables are expressed as the mean and standard deviation. Allelic frequencies were estimated by gene counting, and genotype distribution of the polymorphisms was tested against the Hardy-Weinberg equilibrium by Chi-squared analysis. The association of genotype alleles between women with severe osteoporosis and control group was determined by analysis of Pearson Chi square (χ^2). Crude odds ratios (ORs) were reported with 95% confidence intervals (CI). Where appropriate, *b* allele homozygotes were combined with heterozygotes and the difference in clinical characteristics with and without the *b* allele was compared using the ANOVA test. All calculations were performed using SPSS statistical software version 18.0. The differences were statistically significant at a p value of 0.05 or less.

Results

In this study the data of 73 women was analyzed, including 28 women with severe osteoporosis and 45 control women. The basic descriptive characteristics of study population are provided in Table 1.

Table 1. Basic descriptive characteristics (mean ± SD)

Parameters	Women with severe osteoporosis (n = 28)	Control women (n = 45)	p
Age, years	74.12 ± 6.43	72.9 ± 5.95	0.424
Vitamin D, ng/ml	23.79 ± 14.33	28.47 ± 9.95	0.132
PTH, pg/ml	57.44 ± 24.81	47.32 ± 16.27	0.080
s-CTX-I, ng/ml	0.566 ± 0.276	0.468 ± 0.186	0.086
PINP, ng/ml	79.85 ± 40.44	54.82 ± 20.07	0.001
Lumbar BMD, g/cm^2	0.878 ± 0.146	1.095 ± 0.119	<0.001
Total hip BMD, g/cm^2	0.745 ± 0.097	0.949 ± 0.099	<0.001
Femoral neck BMD, g/cm^2	0.741 ± 0.101	0.869 ± 0.085	<0.001

p – value calculated using Student t-test; SD – standard deviation; PTH – parathyroid hormone; CTX-I – C-terminal cross-linking telopeptide of type I collagen; PINP – procollagen type I N propeptide; BMD – bone mineral density.

It was found that there was no statistically significant difference of age, PTH and s-CTX-I levels between women with severe osteoporosis and controls. The data revealed that PINP in women with severe osteoporosis was significantly higher comparing to the controls. Lumbar spine, total hip and femoral neck BMD was significantly lower in severe osteoporotic women compared to controls.

The frequency of *VDR Bsm*I genotypes in women with severe osteoporosis and control women are shown in Table 2.

Table 2. The frequency of *VDR* BsmI genotypes in women with severe osteoporosis and control women

*VDR Bsm*I genotype	Women with severe osteoporosis (n = 28)	Control women (n = 45)	χ2	p	OR (95% CI)
bb	9 (32.1%)	22 (48.9%)	1.98	0.37	0.50 (0.18–1.33)
Bb	14 (50%)	17 (37.8%)			1.65 (0.63–4.28)
BB	5 (17.9%)	6 (13.3%)			1.41 (0.39–5.15)
b	32 (57.1%)	61 (67.8%)	1.69	0.19	0.63 (0.32–1.26)
B	24 (42.9%)	29 (32.2%)			1.58 (0.79–3.14)

VDR – vitamin D receptor; OR – odds ratio; CI – confidence interval.

It was found that 9 (32.1%) women with severe osteoporosis and 22 (48.9%) control women have *VDR Bsm*I *bb* genotype. *VDR Bsm*I *Bb* genotype was found in 14 (50%) women with severe osteoporosis and 17 (37.8%) control women. The study data revealed that only 5 (17.9%) women with severe osteoporosis, and 6 (13.3%) control women have *VDR Bsm*I *BB* genotype. There was no statistically significant difference of *VDR Bsm*I genotypes between women with severe osteoporosis and control women.

In order to analyze the differences in vitamin D, PTH, serum BTM and BMD by *VDR Bsm*I genotype between women with severe osteoporosis and control groups, study subjects were divided into three groups according to genotype. The results of vitamin D, PTH and BTM levels depending on *VDR Bsm*I genotype are shown in Table 3.

Table 3. Vitamin D, parathyroid hormone, bone turnover markers depending on *VDR* BsmI genotypes in women with severe osteoporosis and control women

Indices	Women with severe osteoporosis by *VDR Bsm*I genotype				Control women by *VDR Bsm*I genotype			
	bb (n = 9)	Bb (n = 14)	BB (n = 5)	p	bb (n = 22)	Bb (n = 17)	BB (n = 6)	p
Vit. D	21.53 ± 12.66	23.39 ± 16.79	23.54 ± 6.58	0.644	29.01 ± 8.5	29.38 ± 12.25	23.54 ± 6.58	0.994
PTH	52.27 ± 18.05	64.38 ± 31.40	50.99 ± 14.08	0.466	43.57 ± 15.41	50.88 ± 17.79	50.99 ± 14.08	0.326
CTX-I	0.551 ± 0.285	0.594 ± 0.314	0.463 ± 0.227	0.896	0.461 ± 0.143	0.479 ± 0.228	0.463 ± 0.227	0.955
PINP	76.56 ± 25.83	85.39 ± 54.38	65.88 ± 19.86	0.826	51.14 ± 12.63	55.66 ± 26.65	65.88 ± 19.86	0.280

Results are expressed as mean ± standard deviation; p value was calculated using ANOVA test and post hoc LSD criterion; VDR – vitamin D receptor; PTH – parathyroid hormone; CTX-I – C-terminal cross-linking telopeptide of type I collagen; PINP – procollagen type I N propeptide.

It was found that total hip and femoral neck BMD is not significantly different between *Bsm*I genotypes in women with severe osteoporosis and control women. However, the lumbar spine BMD is significantly higher in the *BB* genotype as compared to with the *bb* genotype and *Bb* genotype of women with severe osteoporosis (Figure).

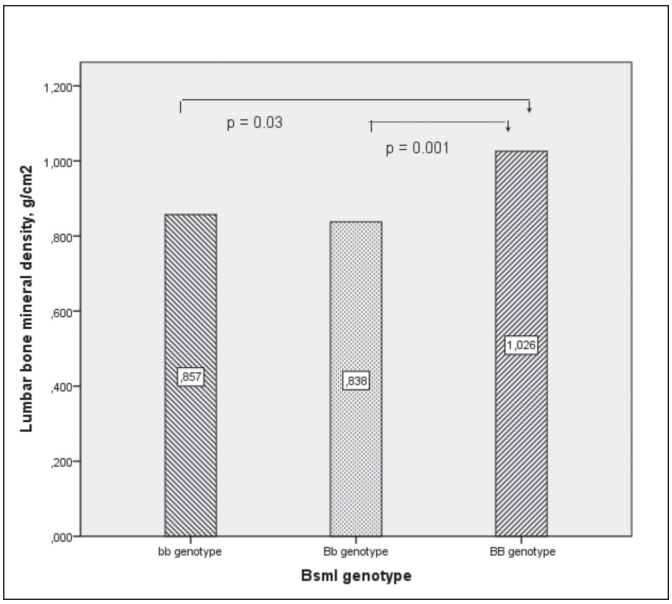

Figure. Lumbar BMD depending on *VDR Bsm*I genotypes in women with severe osteoporosis

The lumbar BMD was not significantly different between *Bsm*I genotypes in control women.

A Spearman's correlation coefficient was calculated to evaluate the correlation between vitamin D, PTH, BTM and BMD depending on *VDR Bsm*I genotype in women with severe osteoporosis and control women. Data are presented in Table 4.

The table shows that in women with severe osteoporosis vitamin D concentration is moderately negatively related to PTH, and PINP is positively related with s-CTXI, also vitamin D is moderately positively related to femoral neck BMD in *VDR Bsm*I *bb* genotype bearers. Our data also revealed that in women with severe osteoporosis PINP is positively related with s-CTX-I in *VDR Bsm*I *Bb* genotype.

Correlation analysis was performed between vitamin D, PTH, BTM and BMD depending on *VDR Bsm*I genotype in control women (table 5).

Our data revealed that in control women carrying *VDR* BsmI bb genotype, PTH level moderately positively related to PINP and s-CTX-I. In control women with *VDR Bsm*I *Bb* genotype, PINP is positively related with s-CTXI. There were no statistically significant correlations between lumbar BMD and total hip BMD and biochemical bone markers in *bb* or *Bb* genotypes either in women with severe osteoporosis or in control women.

Table 4. Spearman's correlation between vitamin D, parathyroid hormone, bone turnover markers and bone mineral density depending on *VDR Bsm*I genotypes in women with severe osteoporosis

Parameters	Vitamin D		PTH		s-CTX-I		PINP	
	r	p	r	p	r	p	r	p
***bb* genotype (n = 9)**								
Vitamin D	–	–	–0.76	0.02	–0.63	0.07	–0.5	0.17
PTH	–0.76	0.02	–	–	0.50	0.17	0.43	0.24
s-CTX-I	–0.63	0.07	0.50	0.17	–	–	0.75	0.02
Lumbar BMD	–0.23	0.55	0.18	0.64	0.51	0.15	0.23	0.55
Total hip BMD	0.55	0.13	–0.58	0.10	–0.56	0.11	–0.55	0.13
Femoral neck BMD	0.66	0.05	–0.33	0.38	–0.2	0.61	–0.11	0.77
***Bb* genotype (n = 14)**								
Vitamin D	–	–	0.40	0.60	–0.80	0.20	–0.20	0.80
PTH	0.40	0.60	–	–	0.35	0.29	0.38	0.24
s-CTX-I	–0.80	0.20	0.35	0.29	–	–	0.89	0.001
PINP	–0.2	0.80	0.38	0.24	0.89	0.001	–	–
Lumbar BMD	0.63	0.37	–0.73	0.83	–0.35	0.29	–0.29	0.38
Total hip BMD	0.4	0.60	0.11	0.75	–0.35	0.29	–0.4	0.22
Femoral neck BMD	0.2	0.80	0.19	0.58	–0.27	0.94	–0.82	0.81

Table 5. Spearman's correlation between vitamin D, parathyroid hormone, bone turnover markers and bone mineral density depending on VDR *Bsm*I genotypes in control women

Parameters	Vitamin D		PTH		s-CTX-I		PINP	
	r	p	r	p	r	p	r	p
***bb* genotype (n = 22)**								
Vitamin D	–	–	0.02	0.92	0.26	0.28	–0.08	0.75
PTH	0.02	0.92	–	–	0.50	0.02	0.45	0.04
s-CTX-I	0.26	0.28	0.50	0.02	–	–	0.64	<0.001
PINP	–0.08	0.75	0.45	0.04	0.64	<0.001	–	–
Lumbar BMD	0.22	0.36	0.11	0.62	0.01	0.99	0.21	0.35
Total hip BMD	0.09	0.72	0.02	0.94	0.04	0.88	0.03	0.91
Femoral neck BMD	0.22	0.36	-0.10	0.65	-0.21	0.35	–0.01	0.97
***Bb* genotype (n = 17)**								
Vitamin D	–	–	–0.18	0.51	0.21	0.44	0.16	0.55
PTH	–0.18	0.51	–	–	0.20	0.44	0.43	0.09
s-CTX-I	0.21	0.44	0.20	0.44	–	–	0.77	0.001
PINP	0.16	0.55	0.43	0.09	0.77	0.001	–	–
Lumbar BMD	0.57	0.20	0.30	0.25	–0.33	0.20	–0.20	0.44
Total hip BMD	0.01	0.98	0.23	0.37	–0.40	0.11	–0.20	0.43
Femoral neck BMD	0.24	0.36	0.04	0.88	–0.28	0.28	–0.11	0.69

Discussion

Osteoporosis represents a significant threat to the health and well-being of aging women. Fracture risk increases exponentially in the elderly with the age-specific incidence of hip fracture. Genetic association studies in osteoporosis often bring discrepant results. As noted by S. Ferrari, "*VDR* association with BMD has been highly controversial, as there are probably as many positive as negative studies" [17]. Conflicting results have been encountered on the role of *VDR* gene polymorphisms in the determination of bone mass, bone turnover, and fracture rate in women [18, 19]. In particular, it is not clear whether the impact of the *VDR* gene variants on bone mass is primarily through effects on achieved peak bone mass and / or on bone loss. In addition to a role in bone metabolism, *VDR* gene polymorphisms may also affect bone mineral density and fracture risk indirectly. It should be noted that vitamin D receptors have been identified on many other tissues including skeletal muscle [20].

We have not found any significant difference of *VDR Bsm*I genotypes between women with severe osteoporosis and control women. Our results are consistent with meta-analyses by A. G. Uitterlinden [21] and Y. Fang [22], where no relationship between *Bsm*I, *Apa*I, *Taq*I and *Foq*I polymorphisms with fracture risk was found.

Recent studies have shown that five polymorphisms and their haplotypes in the population of over 3,000 women failed to show a relationship with BMD or fracture, although with only 248 validated fractures, the latter analysis was underpowered [23]. Also some studies have shown a relationship between *VDR* and risk of fracture, which was independent of BMD, but the mechanism by which *VDR* influences fracture risk was not determined [24, 25]. On the basis of the candidate gene approach, N. A. Morrison et al. first demonstrated a linkage and association between variation in BMD and common variation in polymorphic sites located in exons 8 and 9 at the 3' end of the *VDR* gene (detected by *Bsm*I, *Taq*I, and *Apa*I restriction enzymes) [12, 26]. Despite there being a problem of genotyping in the sample, the association between BsmI genotypes and BMD was still significant [26]. Contrary, our data do not show any statistically significant correlations between lumbar or total hip BMD and BMT in women with severe osteoporosis and in control group. Only the level of vitamin D is moderately positively associated with femoral neck BMD in bb genotype in women with severe osteoporosis.

Subsequently to the discovery of the *VDR* gene, several studies have attempted to validate the association with contradictory findings [27]. A meta-analysis of 75 studies published between 1994 and 1998 concluded that there was a positive association between *VDR* genotypes and BMD though the magnitude of association was lower than the initial report [28].

*Bsm*I polymorphism contains restriction site marked as b allele. According to different studies [29], up to 16% of Caucasians are homozygote for a functionally defective allele of this gene (*BB*) and are at risk of osteoporosis and osteoporotic fractures. In present study, the frequency of BB allele in control group (13.3%) was very similar.

Previous publications on *VDR* gene polymorphisms have focused predominantly on the association with BMD, whereas the data has been limited and has lacked adequate information on bone turnover [15].

In our previous analysis of Belarus population, we have found that *VDR Apa*I, *Bsm*I and *LCT T-13910C* polymorphisms are likely to influence the risk of postmenopausal osteoporosis and make the greatest contribution to its development in Belarusian population. A statistically significant correlation between *VDR Apa*I and *VDR Taq*I risk genotypes and BMD level was also observed.

In present study, the frequency of *BB* homozygote was 17.9%, which is 1.3 times higher in patients group as compared to controls, indicating its association with increased risk of osteoporosis, but not statistically significantly. The frequency of *Bb* genotype was also higher in group of patients with postmenopausal osteoporosis compared to controls. The probability for patients to have such genotypes is also 1.3 times higher comparing to control population. In total, the risk of osteoporosis is 1.6 times higher for risk (*B*) allele bearers comparing to controls, but non statistically significantly. And again, there is a tendency for a decrease of osteoporosis risk between bb-genotype bearers in both groups. Such weak non-significant association of *VDR Bsm*I gene polymorphism may be explained by insufficient number of subjects investigated.

The fact that lumbar BMD was significantly higher in the *BB* genotype as compareg with the *bb* genotype and *Bb* genotype in women with severe osteoporosis, is surprising. Possible explanation could be again the insufficient number of subjects investigated. Also, further analysis of other osteoporosis gene polymorphisms frequency in patients with severe postmenopausal osteoporosis may help to elucidate their association with BMD level more precisely.

Screening of these genetic markers may enable early identification of risk groups to perform preventive measures in a timely manner and also to improve treatment effective-

ness, avoid complications, reduce disability and mortality of these patients, as well as cut down the treatment costs. Physicians of various specialities, for their successful practice, must have complete knowledge about the influence of the polymorphisms in human genes on the development of pathological processes.

Conclusions

The findings of this study suggest that *VDR Bsm*I gene polymorphism has weak non-significant association with BMD level and severe postmenopausal osteoporosis, and the further analyzis is needed. In patients with severe postmenopausal osteoporosis, the lumbar spine BMD was significantly higher in the *BB* genotype bearers as compared to the *bb* and *Bb* genotype bearers. Our research prompts the further large-scale association study of postmenopausal osteoporosis predisposition genes with larger sample sizes and in relation to fracture risk and environmental factors.

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*VDR Bsm*I GENO POLIMORFIZMO SĄSAJOS SU KAULINIO AUDINIO REMODELIACIJOS BIOCHEMINIAIS ŽYMENIMIS IR KAULŲ MINERALŲ TANKIU MOTERIMS SERGANČIOSIOMS SUNKIA POMENOPAUZINE OSTEOPOROZE

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Santrauka

Vitamino D receptoriaus (*VDR*) geno sąsajos su mažesniu kaulų mineralų tankiu ir didesne kaulų lūžių rizika yra neaiškios.

Tikslas – nustatyti *VDR* geno *Bsm*I polimorfizmo ir kaulų apykaitos žymenų, kaulų mineralų tankio sąsajas moterims, sergančioms sunkia pomenopauzine osteoporoze.

Tiriamųjų kontingentas ir metodai. Vitamino D, paratiroidinio hormono, kaulų apykaitos žymenų tyrimai buvo atlikti taikant elektrocheminės liuminescencijos metodą, *VDR Bsm*I geno polimorfizmas buvo nustatytas taikant polimerazės grandininę reakciją. Kaulų mineralų tankis buvo matuotas dvigubos radioabsorbciometrijos metodu. Skirtumai tarp tirtų grupių nustatyti taikant ANOVA testą, atlikta subgrupių papildoma statistinė koreliacinė analizė.

Rezultatai. Šiame tyrime analizuoti 73 moterų duomenys, iš jų 28 sirgo sunkia pomenopauzine osteoporoze ir 45 moterys buvo kontrolinėje grupėje. *VDR* geno *Bsm*I genotipų reikšmingų skirtumų nenustatyta lyginant sunkia sergančias osteoporoze moteris su kontroline grupe. Taip pat nenustatyta reikšmingų koreliacinių ryšių esant *bb* ir *Bb* genotipams tarp stuburo ir bendro šlaunikaulio kaulų mineralų tankio bei kaulų apykaitos žymenų sergančioms sunkia osteoporoze ir kontrolinės grupės moterims. Tačiau sunkios osteoporozės tiriamųjų grupėje *BB* genotipo nešiotojoms rastas reikšmingai didesnis stuburo srities kaulų mineralų tankis, negu esant *bb* ar Bb genotipui. Moterims su *VDR Bsm*I *bb* genotipu vitamino D koncentracija neigiamai koreliavo su paratiroidinio hormono koncentracija ir teigiamai koreliavo su šlaunikaulio kaklo kaulų mineralų tankiu. PINP teigiamai koreliavo su s-CTX-I moterims, sergančioms sunkia pomenopauzine osteoporoze.

Išvados. *VDR Bsm*I geno polimorfizmas nereikšmingai silpnai koreliuoja su kaulų mineralų tankiu. Tačiau esant sunkiai pomenopauzinei osteoporozei, *BB* genotipo nešiotojoms stuburo srities kaulų mineralų tankis buvo reikšmingai didesnis, negu esant *bb* ar *Bb* genotipui. Reikalingi tolimesni sunkios pomenopauzinės osteoporozės genetiniai tyrimai.

Raktažodžiai:

VDR genas, polimorfizmas, kaulinio audinio apykaitos žymenys, kaulų mineralų tankis, sunki pomenopauzinė osteoporozė