

Research Article

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Association between Vitamin D Receptor Gene Polymorphism, Secondary Hyperparathyroidism and Ultrasound Densitometry Parameters in Postmenopausal Women

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Abstract

Background

Many studies have confirmed that the vitamin D receptor (VDR) polymorphism might be associated with the risk of systemic osteoporosis and its complications. The aim of the study was to find out the association between VDR gene polymorphism and secondary hyperparathyroidism and bone tissue status in postmenopausal women.

Patients and methods

178 postmenopausal women (mean age 57.0 ± 1.2 years) were examined from the western (36.5%), eastern (24.7%) and northern (38.8%) regions of Ukraine. Vitamin D receptor polymorphisms were defined using the RFLP reaction. After the analysis, samples were classified as BB, Bb or bb. The serum content of 25(OH) vitamin D (25(OH)D) and intact parathyroid hormone (iPTH) were defined by electrochemiluminescence method. All examined patients underwent ultrasonic calcaneal densitometry.

Results

Women with a genotype Bb had lower percentage of osteoporosis and low-energy fractures. Women, who live in the east of Ukraine, more often are carriers of genotype BB (20.5%), have a higher risk of fractures, vitamin D deficiency and secondary hyperparathyroidism. Patients who carry bb genotype have a higher risk of osteoporosis and secondary hyperparathyroidism.

Conclusion

Genetic variations in VDR are significantly associated with vitamin D deficiency, secondary hyperparathyroidism and osteoporosis among Ukrainian postmenopausal women. Further studies are required to confirm the role of the VDR polymorphisms in development of postmenopausal osteoporosis in older women.

Keywords: Vitamin D receptor gene; Polymorphism; Vitamin D deficiency; Secondary hyperparathyroidism; Bone; Ultrasound densitometry; Postmenopausal women

Introduction

Nowadays, many studies have investigated the association between genetic variants and osteoporosis and its complications. Some researchers have confirmed that the vitamin D receptor polymorphism might be associated with the risk of systemic osteoporosis [1-5]. However, there is no single view on the association between the polymorphism of certain genes and the bone tissue state, since in some scientific works such a correlation is found, in others no [5]. Differences in the results of studies are explained by differences in the genome structure, in characteristics of people's nutrition (primarily in the level of calcium and vitamin D consumption), as well as the impact

of environmental factors on the human body in different regions of the world [6].

Vitamin D receptors (VDRs) belong to nuclear intracellular receptors (which also include receptors for steroid hormones, thyroid glands hormones and retinoic acid), subtype PPX. This group of receptors regulates expression of genes that control the functions of proliferation, differentiation, metabolism, transport of ions, apoptosis, etc. [7,8].

VDRs have high affinity to the hormonal form of vitamin D-1,25(OH)₂D₃. The secretion of the latter depends on the body's needs for calcium and phosphorus. In hypocalcemia, the level of parathyroid hormone increases, that stimulates activity of renal 1 α -hydroxylase and contributes to the synthesis of 1,25(OH)₂D₃. 1,25(OH)₂D₃ binds to VDR and increases calcium absorption in the small intestine by means of TRPV6 and other genes of calcium translocation [9;10].

Despite the data that polymorphism of the vitamin D receptor (VDR) gene plays an important role in variations for genetic regulation of bone mass and development of osteoporosis in postmenopausal women, its role within various ethnic populations is not clear. The aim of the study was to find out the association between VDR gene polymorphism and secondary hyperparathyroidism and bone tissue status (BTS) in postmenopausal women.

Materials and Methods

The study was conducted as a part of Research work which was performed in Department of clinical physiology and pathology of the musculoskeletal systems of the D. F. Chebotarev Institute of Gerontology NAMS Ukraine (Kyiv) "Development of complex program for the diagnosis, prevention and treatment of vitamin D deficiency and insufficiency in patients of older age groups with bone and muscular diseases" (The number of registration: 0112U000526). All patients signed informed consent for participation in the study. We utilized a cross-sectional research design.

178 postmenopausal women were examined. The average age was (57.0 ± 1.2) years old. The study included residents from the western (36.5%), eastern (24.7%) and northern (38.8%) regions of Ukraine.

Vitamin D receptor polymorphisms were defined using the RLFP (Restricted Length Fragment Polymorphism) reaction, which provides the definition of point mutations using specific endonuclease Bsm I, the last was added to the samples after the amplification procedure. After the analysis, samples were classified as BB, Bb or bb (capital letters indicate absence, small ones point the presence of restriction sites for endonuclease Bsm I).

The serum content of 25(OH) vitamin D (25(OH)D) and intact parathyroid hormone (iPTH) were defined by electrochemiluminescence method on the ElecSys 2010 analyzer (Roche Diagnostics, Germany) using cobas test-systems.

The assessment of vitamin D status was performed according to the latest classification [11]: vitamin D deficiency (VDD) was established at 25(OH)D content in blood serum below 50 nmol/L, vitamin D insufficiency was detected at serum levels of 25(OH)D between 75 and 50 nmol/L. The serum concentration of 25(OH)D within the range of 75-150 nmol/L is considered normal. Severe VDD is considered when the level of 25(OH)D in serum is below 25 nmol/L.

All examined patients underwent ultrasonic calcaneal densitometry on SAHARA apparatus (Hologic), determined the speed of ultrasound propagation through bone (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz), stiffness index (SI, %) and an extrapolated index of bone mineral density (eBMD).

Statistical analysis was carried out with the definition of parametric and nonparametric criteria using software packages "Statistics 6.0", Copyright © StatSoft, Inc. 1984-2001, Serial number 31415926535897.

Results

According to VDR gene polymorphism studies, all patients were divided into three groups: the first with genotype bb-86 patients, the second with the genotype Bb-67 patients, and the third included 25 women with the genotype BB.

Clinical characteristics of the examined patients are presented in Table 1. There were not significant differences between main indicators of the groups.

| Genotype Indicator | bb, % | Bb, % | BB, % |
|------------------------|--------------|--------------|--------------|
| n | 86 | 67 | 25 |
| Age, years | 57.49 ± 1.74 | 56.74 ± 2.04 | 56.23 ± 3.21 |
| Height, cm | 163.5 ± 0.85 | 163.9 ± 0.74 | 165.8 ± 1.83 |
| Weight, kg | 74.05 ± 2.01 | 78.02 ± 1.76 | 79.08 ± 2.83 |
| BMI, kg/m ² | 27.57 ± 0.65 | 29.17 ± 0.73 | 28.69 ± 0.81 |

Table 1: Clinical characteristics of women depending on vitamin D receptor polymorphisms.

The serum level of 25(OH)D was normal in 4.5% of the examined women, insufficiency was identified in 10.1%, and deficiency-in 85.4% of cases. 46.6% of the patients have a severe VDD.

Secondary hyperparathyroidism was detected in 29.2% of examined women. Elevated levels of iPTH among examined women were registered because in the northern regions group mostly women with secondary hyperparathyroidism were included for studying the role of VDR gene polymorphism. Osteoporosis was registered in 28 (15.7%) patients, osteopenia in 31.5%, and normal BTS in 94 (52.8%) of examined persons. 28.7% of the patients have previous low-energy fractures.

The studying of VDR gene polymorphism showed that bb genotype was detected in 86 (48.3%) of the examined, Bb was registered in 67 (37.6%), and the BB genotype occurred in 25 (14.1%) subjects.

As shown in Table 2, the VDR gene polymorphism bb was registered with the same frequency among residents of the western, eastern and the northern regions (46.2, 47.7 and 44.7% respectively). The VDR gene polymorphism BB was higher (20.5%) among inhabitants of the eastern regions and almost twice lowers among the inhabitants of northern regions (10.5%) and equally often recorded both in women of the western and central regions.

| Region of study | Genotype | | |
|-----------------|----------|-------|-------|
| | bb, % | Bb, % | BB, % |
| West, n=65 | 46.2 | 41.5 | 12.3 |
| East, n=44 | 47.7 | 31.8 | 20.5 |
| North, n=38 | 44.7 | 42.1 | 10.5 |

Table 2: Distribution of the examined patients according to VDR gene polymorphisms.

Patient's characteristics depending on the genotype are listed in Table 3. Analysis of the data presented in table shows that patients were not significantly different in age. Also, there was no significant difference in the mean serum level of 25(OH)D and iPTH of the examined patients.

A comparative analysis of osteoporosis frequency, fractures, secondary hyperparathyroidism, vitamin D deficiency and severe vitamin D deficiency, depending on the genotype of subjects, was conducted (Table 3).

| Indicator | Genotype | | |
|----------------------------------|--------------|--------------|--------------|
| | bb, % | Bb, % | BB, % |
| Age, years | 57.49 ± 1.74 | 56.74 ± 2.04 | 56.23 ± 3.21 |
| 25(OH)D, nmol/L | 31.78 ± 2.52 | 31.97 ± 2.31 | 25.92 ± 2.64 |
| iPTH, pg/mL | 53.45 ± 2.41 | 52.15 ± 2.79 | 53.45 ± 3.75 |
| Osteoporosis, % | 22.1 | 7.4 | 16.0 |
| Fractures, % | 27.4 | 23.1 | 29.2 |
| VDD, % | 82.6 | 85.1 | 96.0 |
| Severe VDD, % | 48.8 | 41.8 | 52.0 |
| Secondary hyperparathyroidism, % | 29.1 | 28.4 | 32.0 |

Table 3: Characteristics of the examined patients according to VDR gene polymorphisms.

It was found out that the genotype Bb was characterized by the lowest frequency of osteoporosis (7.4%) versus 22.1% for genotype bb and fractures (23.1% vs. 29.2% for genotype BB). Women with genotype bb were found to have a higher percentage of osteoporosis (22.1%), while carriers of the genotype BB have a higher percentage of fractures (29.2%).

The highest percentage of VDD (96% vs. 82.6% in genotype bb) and secondary hyperparathyroidism was recorded in patients with the genotype BB (32.0% versus 28.4% in genotype Bb). Carriers of the genotype BB suffered more frequent from severe VDD (52%) against people with genotype Bb (41.8%). Ultrasound densitometry indices were higher in examined patients with genotype Bb and significantly differed from those with genotype bb (Table 4).

| Indicator | Genotype | | |
|-------------------------|-------------------------|---------------------------|--------------------------|
| | bb, % | Bb, % | BB, % |
| n | 86 | 67 | 25 |
| T-score | -1.70 [-2.20; -0.90] | -0.90** [-1.60; -0.55] | -0.95* [-1.40; -0.40] |
| SI, % | 81.59 ± 2.15 | 87.78 ± 1.95* | 86.82 ± 3.23 |
| eBMD, g/cm ² | 0.440 ± 0.014 | 0.479 ± 0.012* | 0.473 ± 0.020 |
| SOS, m/s | 1527.1 ± 3.6 | 1535.4 ± 3,2 | 1533.8 ± 5.9 |
| BUA, dB/MHz | 64.53 ± 1.87 | 71.41 ± 1,89* | 70.69 ± 2.76 |

Table 4: Indices of bone tissue status in postmenopausal women with different VDR genotype.

Thus, women with a genotype Bb had lower percentage of osteoporosis and fractures. Women who live in the east more often are carriers of genotype BB (20.5%), have a higher risk of fractures, VDD, severe VDD, and secondary hyperparathyroidism. Individuals who carry bb genotype have a higher risk of osteoporosis and secondary hyperparathyroidism.

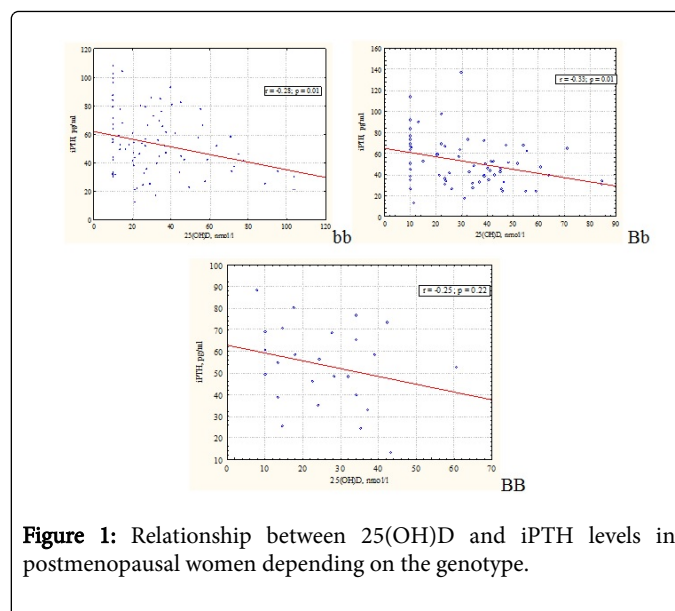


Figure 1: Relationship between 25(OH)D and iPTH levels in postmenopausal women depending on the genotype.

Results of the dispersion analysis of the relationship between serum level of the 25(OH)D and iPTH in examined women are presented on Figure 1.

Discussion

Nowadays, many studies have investigated the relationship between VDR gene polymorphism and risk of systemic osteoporosis and its complications, however the results are controversial [12-14] and role of VDR polymorphism in various ethnic populations is not clear.

Wu et al. [1] showed the significant differences in the Ward's triangle bone mineral density (BMD) indices among VDR gene ApaI polymorphisms (p<0.05), aa genotype was connected with significant lower BMD indices, however no significant difference among the different genotypes and occurrence of osteoporosis with osteoporotic fracture was established.

Langdahl et al. [3] studied four polymorphisms Fok I (T2-C), Bsm I (intron 8), Apa I (intron 8) and Taq I (T1055-C). Authors did not find any association between the Fok I polymorphism and bone mass, bone turnover and prevalence of osteoporotic fractures. However, BMD of the intertrochanteric region (p<0.0001) and total hip (p<0.01) were higher in patients with the bb-genotype. The Apa I and the Taq I polymorphisms were not distributed differently among osteoporotic patients and normal controls. Another study was performed in Turkey [13], the frequencies BsmI and Taq genotypes were studied. It was established that genotype frequencies of VDR were not statistically different between patients with osteoporosis and the control group. Among VDR haplotypes, bbAATT and bbTtAa are more frequent in the osteoporosis group than the control group.

Mohammadi et al. [5] performed the literature review from different databases and assess papers published between 2000 and 2013 which describe the association between FokI and BsmI polymorphisms of the VDR gene and osteoporosis risk. They demonstrate that more than 50% studies reported significant relation between FokI, BsmI and osteoporosis.

Another meta-analysis which analyzed the relationship of vitamin D receptor polymorphism and risk of osteoporosis was performed by

Zhao B et al. [2]. Ten case-control studies, 1 403 osteoporosis cases and 2 144 healthy controls were included. Authors did not find the significant correlation between BsmI polymorphism and risk of osteoporosis (BB vs. bb: odd ratio (OR)=0.76, 95% confidence interval (CI)=0.39–1.48; BB vs. Bb: OR=0.90, 95% CI=0.71–1.15; dominant model: OR=1.20, 95% CI=0.74–1.93; recessive model: OR=0.83, 95% CI=0.53–1.30). In the subgroup analysis by ethnicity it was demonstrated the similar results.

Moran et al. [4] also studied the relationship between VDR polymorphisms and osteoporosis through a systematic review of the literature. Authors demonstrated that no definite conclusions can be made regarding the association of BsmI, ApaI, FokI, and TaqI polymorphisms with BMD among postmenopausal women.

Our study was aimed to find out the association between VDR gene polymorphism, frequency of vitamin D deficiency, secondary hyperparathyroidism and bone tissue deteriorations in postmenopausal women.

According our results, patients with a genotype Bb have better Ultrasound densitometry data and, consequently, have a lower percentage of systemic osteoporosis and fractures. Women who live in the east of Ukraine more often are carriers of genotype BB, have a higher risk of low-energy fractures, VDD, severe VDD, and secondary hyperparathyroidism. In addition, individuals who carry bb genotype have a higher risk of osteoporosis and secondary hyperparathyroidism.

Moreover, we established the significant negative correlation between 25(OH)D and iPTH serum levels in individuals with genotype bb, it was ranged ($r=-0.28$, $p<0.01$). The relationship between serum 25(OH)D and iPTH levels was also reliable negative in the Bb-examined genotypes, but still moderate ($r=-0.33$, $p<0.01$). In contrast, the relationship between levels of 25(OH)D and iPTH in serum was not detected in women with genotype BB.

Thus, we confirmed that women of genotype Bb have significantly higher rates of bone tissue status, such as stiffness index ($p<0.05$), eBMD ($p<0.05$) and SOS ($p<0.05$) compared to women who are carriers of the genotype bb. Women with genotype Bb have lower frequency of osteoporosis, fractures and secondary hyperparathyroidism. It has been established that there is no association between serum level of 25(OH)D and iPTH in women with genotype BB, however, there is a correlation in women who carry the bb ($r=-0.28$, $p<0.01$) and Bb ($r=-0.33$, $p<0.01$) genotype.

Our results are confirmed by studies by other researchers. So, P. Garnero et al. [12] studied the association between VDR gene polymorphism and vertebral and nonvertebral fractures. The authors found association between the increasing of allele B frequency in women with the first recorded fractures. The relative risk of such fractures for women with genotype Bb was 1.5 (95% CI: 0.95-2.40), and in the case of genotype BB–2.10 (95% CI 1.16-3.79) compared to women with genotype bb.

Pishel [15] found out the significant relation between the incidence of fractures and bb genotype of VDR gene (BsmI; 51.0%) in Ukrainian postmenopausal women. The relative risk of fracture in patients with this genotype in comparison with allele B carriers (BB/bb) was 1.76 (95% CI: 1.14-2.70, $p<0.02$). The relationship between genotype and bone mineral density has not been demonstrated in this observation.

Conclusion

The association between vitamin D receptor gene polymorphism and the bone tissue status is established. The carriers of the Bb genotype are characterized by higher bone mineral density, which determine the low percentage of osteoporosis and its complications (fractures), the lowest frequency of severe vitamin D deficiency and secondary hyperparathyroidism.

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