International Journal of Neuroscience and Research
An open access journal
eSciRes
ISSN 2578-4870
Research Article
IJNR-3-107

Relationship Between BMD Reduction and *VDR* Gene Polymorphism in Patients with Epilepsy

Xue-lian Chen[1], Jing-yuan Wu[2], Wen-qiang Zhong[1], Yan Chen[1], Jia He[1], Hai-yan Gou[1] and Yan-mei Zhu[1]*

[1]Department of Epilepsy and Sleep Disorder, Second Affiliated Hospital of Harbin Medical University,246 Xuefu Road,150086, Harbin, China

[2]Stroke Center, the Fourth Affiliated Hospital of Harbin Medical University, No.37 Yiyuan Street,150001, Harbin, China

Abstract

Purpose: To investigate the relationship between decreased Bone mineral density (BMD) and vitamin D receptor (VDR) gene polymorphism in patients with epilepsy. To evaluate whether there is an association between VDR-FokI and VDR-TaqI sites in patients with epilepsy after long-term use of antiepileptic drugs, and to analyze related risk factors affecting BMD reduction in patients with epilepsy. **Methods:** From September 2020 to November 2021, 50 hospitalized patients in the Epilepsy Center of the Second Affiliated Hospital of Harbin Medical University were screened. All enrolled patients met the diagnostic criteria for epilepsy proposed by the International League against Epilepsy in 2016. All patients were treated with monotherapy and had been taking medication continuously for at least 1 year. Patients with known systemic diseases (eg. obvious abnormalities in thyroid function and kidney function), taking osteoporosis-inducing drugs (eg. oral glucocorticoids), and adverse lifestyle habits affecting BMD (eg. heavy smoking and alcohol abuse) were excluded. General clinical data of patients were collected, including gender, age, course of disease, type of medication, and duration of medication. BMD of lumbar spine and hip joint was detected by BMD detector. The criteria for determining BMD according to T value are as follows: normal bone mass: T value >-1; Low bone mass: -2.5 < T value ≤ -1; Osteoporosis: T ≤ -2.5. Whole peripheral venous blood was extracted, DNA was amplified by polymerase chain reaction (PCR), genotyping was performed by enzyme digestion technology, and *VDR-TaqI* and *VDR-FokI* gene detection results were obtained. In the process of data statistics, gender, age, course of disease, type of medication, duration of medication, VDR-TaqI and VDR-FokI were used as independent variables, and BMD reduction of lumbar spine and hip joint was used as dependent variables, respectively. To explore the correlation between the polymorphism of VDR-TaqI and VDR-FokI and reduced BMD of lumbar spine and hip joint in patients with epilepsy. **Results:** Among 50 patients, 21 were in the normal BMD group and 29 were in the reduced BMD group. Comparison of general and clinical data between the two groups showed that the duration of disease ≥10 years, duration of medication ≥5 years, the proportion of TaqI (TT), TaqI (Tt), FokI (FF), FokI (ff) in the reduced lumbar BMD group was higher than that in the normal BMD group, and the distribution difference was statistically significant (P < 0.05).Univariate Logistic regression analysis showed that VDR-TaqI, duration of disease and duration of medication were correlated with the reduction of lumbar BMD in patients with epilepsy (P<0.05). Multifactor stepwise Logistic regression analysis showed that age, duration of medication and VDR-TaqI were significantly related to the reduction of lumbar BMD in epilepsy patients. The average BMD values of TT, Tt and tt patients were -2.75 ± 0.073, -1.37 ± 0.399 and 0.09 ± 1.42, respectively, indicating that the lumbar BMD values were the lowest in patients with TT genotype and the highest in patients with tt genotype. Using TaqI (tt) as reference, the risk of lumbar BMD reduction gradually increased with the increase of T allele, suggesting that T allele was a risk factor for BMD reduction in epilepsy patients (P<0.05, OR =279.56). There was no significant correlation between VDR-FokI site and lower BMD in the lumbar spine of patients. The average BMD of the three groups of FokI (Ff), FokI (ff) and FokI (ff) was -1.35 ± 0.2, -0.33 ± 1.4, and -2.03 ± 0.71, respectively. There was no significant difference in BMD among the three groups (P>0.05). Among the 50 patients, 23 had normal hip BMD and 27 had reduced hip BMD. General and clinical data were compared between the two groups. The results showed that the duration of disease ≥ 10 years, the proportion of TaqI (TT), TaqI (Tt), FokI (FF) and FokI (ff) in the reduced hip joint BMD group was higher than that in the normal hip joint BMD group, and the distribution difference was statistically significant (P<0.05). Univariate Logistic regression analysis showed that VDR-TaqI and disease duration were correlated with decreased hip BMD (P<0.05). Multivariate stepwise Logistic regression analysis showed that disease duration and VDR-TaqI genotype were significantly associated with decreased hip BMD in epilepsy patients. The mean hip BMD values of TT, Tt and tt genotype patients were -2.6 ± 0.073, -1.39 ± 0.49 and 0.09 ± 1.38, respectively, that is, the hip BMD values of TT genotype patients were the lowest and those of tt genotype patients were the highest. Using TaqI (tt) as reference, the risk of hip BMD reduction gradually increased with the increase of T allele, suggesting that T allele was a risk factor for hip BMD reduction in epilepsy patients (P > 0.05, OR values were 40.858, respectively). The above regression analysis showed no significant association between VDR-FokI sites and decreased hip BMD in epilepsy patients. The mean hip BMD values of FokI (FF), FokI (Ff), and FokI (ff) groups were -1.52 ± 0.32, 0.32 ± 1.40, and -1.77 ± 1.1, respectively, and there was no significant difference in BMD values among the three groups (P>0.05). **Conclusion:** The potential pathogenesis of reduced BMD in patients with epilepsy may be related to VDR gene polymorphism: VDR-TaqI is associated with decreased BMD in hip and lumbar spine, and T allele is a risk factor for decreased BMD in patients with epilepsy. Patients with TT genotype have the lowest BMD value and those with tt genotype have the highest BMD value. There was no significant correlation between VDR-FokI and BMD of hip and lumbar spine in epileptic patients.

Keywords: Epilepsy; Vitamin d receptor; VDR-TaqI gene polymorphism; VDR-FokI gene polymorphism; Bone density

Epilepsy (Epilepsy) is a common and frequently occurring disease of the nervous system, affecting about 65 million people in the world. Epidemiological studies show that the annual incidence of Epilepsy is about 0.5‰ in developed countries, while the prevalence is close to 7% [1]. The prevalence of epilepsy in mainland China is 2.89% [2, 3]. Epilepsy itself and its complications and comorbidities in the course of long-term illness will bring great burden and trouble to patients and society. Osteoporosis (OP) is the most common bone disease affecting more than 200 million people worldwide [4]. It is characterized by reduced BMD due to imbalance in bone remodelling process, resulting in impaired bone structural integrity, reduced strength and increased risk of fracture [5]. Previous studies have reported that patients with epilepsy are more prone to vitamin D deficiency, reduced bone mass and increased fracture risk, and the fracture risk of epilepsy patients is 2-6 times higher than that of normal people. Fragility fractures in adult epilepsy patients are associated with significantly increased mortality and heart disease incidence at 3, 6, 12 and 24 months [6,7]. The development of OP in people with epilepsy has been linked to a number of factors, related to the type of epilepsy, falls during seizures, family history, and the presence of diseases that affect bone metabolism. In addition to other risk factors, Anti-seizure medication (ASM) treatment may be another cause of OP. Long-term ASM therapy is an independent risk factor for decreased BMD in at least some patients [8]. Vitamin D (VD) deficiency is often found in patients with epilepsy, Studies have found that vitamin D exists in neurons and glial cells and is a regulator of neuronal excitability and seizure susceptibility [9]. Vitamin D Receptor (VDR) regulates the expression of DNA by binding to its active product 1.25 hydroxylated vitamin D3 (1,25-(OH)2D3) to play a variety of biological functions. System in recent years, the VDR single nucleotide polymorphisms (single nucleotide polymorphism, SNP) research has become a hot spot content, and bone health have a close relationship with epilepsy. As reported by Morrison et al. [10], many candidate genes have been shown to be associated with BMD or fractures [11]. The vitamin D receptor (VDR) gene has been the most extensively studied. Vitamin D deficiency is common in patients with epilepsy, and a possible association between VDR gene polymorphism and bone disease caused by ASM is considered. At present, common *VDR* gene polymorphisms include VDR-ApaI,VDR-BsmI,VDR-TaqI,VDR-FokI,VDR-Cdx2. Previously, our research group also studied the relationship between VDR-BsmI site and decreased BMD in epilepsy patients, and the results found that: the general clinical data and clinical data of lumbar BMD and hip BMD normal group and decreased group were compared, and there was no statistically significant difference in VDR-BsmI between normal group and reduced group (P>0.05).With the reduction of BMD of lumbar spine or hip joint as the dependent variable, and gender, age, course of disease, type of medication, duration of medication and VDR-BsmI as the independent variables, univariate Logistic regression analysis showed that the above variables were not correlated with the reduction of BMD of lumbar joint or hip joint (P>0.05). Conclusion: VDR-BsmI is not associated with lumbar BMD and hip BMD in epileptic patients. However, an earlier study on the association between VDR-BsmI sites and BMD in epilepsy patients showed that VDR-BsmI polymorphism was significantly correlated with decreased bone mass in epilepsy patients who took anti-epileptic drugs for a long time [12]. All patients with BMD lower than the expected age range were BB genotype. And the circulating 25-hydroxyvitamin D3 levels were low. There are some differences between the results of this study and the previous results of our research group, which may be due to the differences in race and genetic background of the study subjects, and may also be related to factors such as the inclusion criteria and sample size. However, studies on the correlation between other genotypes and decreased bone mass in epilepsy patients are scarce. This paper aims to explore the relationship between decreased bone mineral density (BMD) and vitamin D receptor (VDR) gene polymorphism in epilepsy patients. To evaluate whether there is an association between VDR-FokI and VDR-TaqI sites and decreased BMD in epileptic patients after long-term use of antiepileptic drugs (ASM), and to analyze related risk factors for decreased BMD in epileptic patients.

Subjects and Methods

Subjects were selected from 50 patients with epilepsy who were hospitalized in the Department of Neurology and Epilepsy Center of the Second Affiliated Hospital of Harbin Medical University from September 2019 to November 2019.Inclusion criteria: All participants met the criteria for the diagnosis of epilepsy (International League against Epilepsy Diagnostic Criteria 2016) and were treated with monotherapy for a duration of at least 1 year. Other systemic diseases affecting bone mass, adverse lifestyle habits affecting BMD and patients taking drugs affecting BMD were excluded, such as: thyroid function, kidney function and other diseases affecting calcium and phosphorus metabolism, heavy smoking and alcoholism, oral glucocorticoids.

Research Methods

1. Patient information was collected from the patient medical record system of neurology department and epilepsy Center of our hospital, and data such as gender, age, course of disease, medication status (including the duration of ASM treatment and specific drug types) of epilepsy patients were collected.
2. **Auxiliary examination:** BMD measurement method: BMD of lumbar spine and hip joint were detected by dual-energy X-ray BMD instrument during admission of all enrolled subjects.
3. It is necessary to calibrate the detector daily.
4. Enter patient information.
5. The measurement sites were lumbar spine (L2-L4) and proximal femur.
6. BMD analyzer automatically analyzes and generates a report after scanning. Criteria: Normal bone mass: T value >-1; Low bone mass: -2.5<T value ≤ -1; Osteoporosis: T ≤ -2.5. Genotyping of VDR-TaqI and VDR-FokI:

a. Frozen blood samples were taken from 500 μl to 1.5 mL centrifuge tube, centrifuged for 5 min at 2000 RPM, excess supernatant was discarded, and 200 μl supernatant and sediment were retained.

b. Solution GB200 μl, RNaseA (10 mg/ml) 10 μl and Proteinasek 20 μL were added to the above samples, and were fully absorbed and mixed, and then bathed in a water bath for 10min (56°C)

c. Add 200 μl of 100% ethanol and mix thoroughly.

d. Place the adsorption column AC on the collection pipe, move the solution to the adsorption column for 2 min, centrifuge at 12000 RPM, and discard the filtrate.

e. Add solution WA500 μl to AC, centrifuge for 1min at 12000 RPM, and discard filtrate.

f. Add solution WB500 μl to AC, centrifuge for 1min at 12000 RPM, and discard filtrate.

g. Repeat Step b.

h. Place the adsorption column AC on the collection tube again, centrifuge for 2 min at 12000 RPM, and discard the filtrate.

i. Place AC on a new 1.5 ml centrifuge tube, add elution buffer EB55 μl to the center of AC membrane, and let it stand at room temperature for 5min (Note: elution buffer EB is beneficial to improve elution efficiency when heated to 65°C). Centrifuge for 2 min (12000 RPM), eluting DNA. If a larger yield is required, the dissociated solution can be readded to the center of the AC membrane or the elution buffer EB50 μl can be added, and then the above steps are repeated.

j. The obtained DNA is immediately carried out for the next experiment or stored at -20°C.The obtained DNA samples were amplified by PCR. The PCR products were enzymatically digested. The PCR products were detected by electrophoresis using agarose gel with a concentration of 1.5%, and were observed and photographed under the system.

Statistical methods

Spss25.0 was used for statistical analysis; mean standard deviation was used for measurement data subject to normal distribution; ANOVA was used for inter-group comparison; median and interquart interval were used for non-normal distribution; rank sum test was used for inter-group comparison; percentage of cases was used for counting data; Chi-square test was used for inter-group comparison. logistic regression analysis was used to analyze the influencing factors, and P<0.05 was statistically significant.

Results

VDR-TaqI Results

Figure 1 shows the results of VDR-TaqI experiments in some patients: Lane 6 was TT homozygous, with two bands of 512bp and 201bp respectively; Lane 1, 2, 3, 4 and 5 were Tt heterozygotes, and the three strips were 512bp, 311bp and 201bp in size, respectively. Lane 7 and 8 are tt homozygous, and the two strips are 311bp and 201bp in size respectively. See Figure 1 below.

VDR-FokI results

Figure 2 VDR-FokI results of some patients: Lane 4 and 5 were FF homozygous, with a strip size of 267bp; Lane 1, 2, 3 and 8 were Ff heterozygotes, with the sizes of 267 bp, 197bp and 70bp, respectively. Lane 6 and 7 are ff sub bands, the sizes of which are 197 bp and 70 bp respectively, as shown in Figure 2.

Baseline BMD of lumbar spine in epileptic patients

Comparing the general clinical data and clinical data between the normal group and the decreased group of lumbar BMD, the differences in course of disease, medication time, VDR-TaqI and VDR-FokI between the two groups were statistically significant (P<0.05).

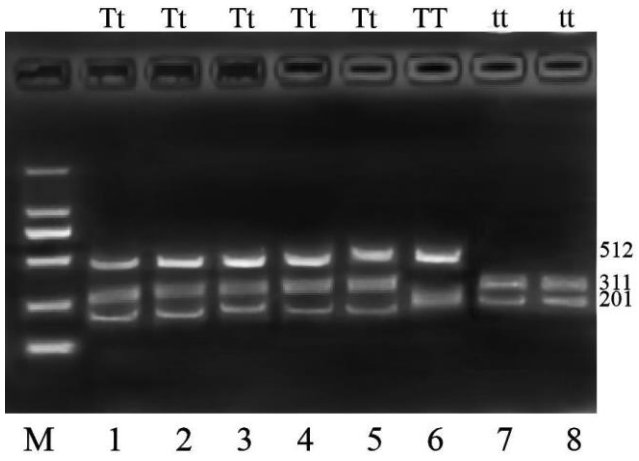

Figure 1: VDR-TaqI agarose gel electrophoresis results, M: Maker.

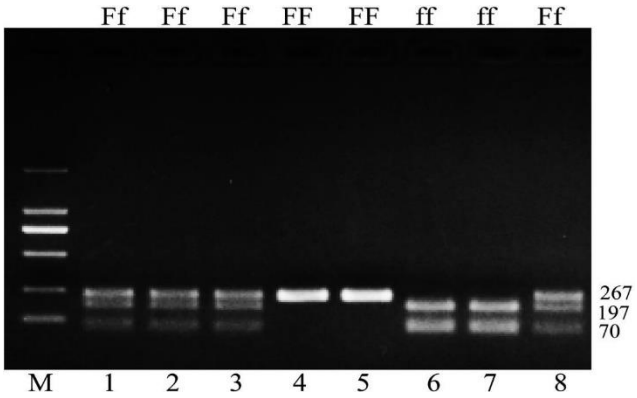

Figure 2: VDR-FokI agarose gel electrophoresis results, M: Maker.

As shown in Table 1: 2 cases of TaqI (TT), All were located in the BMD reduction group (6.9%); 18 Taq I (Tt), 2 (9.52%) in the BMD group, 16 (55.2%); In total, 30 cases of TaqI (tt), 19 (90.5%) in the BMD group, 11 (37.9%); There were 6 cases of FokI (FF), All were located in the BMD reduction group (20.7%); 41 FokI (Ff), Of 21 patients (100%) in the normal BMD group, 20 cases (60.9%); 3 cases of FokI (ff), Are located in the BMD reduction group (10.3%), See the Table 1.

Single factor logistic regression analysis of influencing factors of lumbar

BMD reduction in epileptic patients: With the decrease of lumbar BMD as the dependent variable and sex, age, course of disease, type of medication, medication time, VDR-TaqI and VDR-FokI as the independent variables, the univariate Logistic regression analysis was conducted. The results showed that VDR-TaqI, medication time and course of disease were related to the decrease of lumbar BMD in epileptic patients, and T allele was the risk factor for the decrease of BMD (P<0.05), as shown in Table 2.

Variable	Normal Group of BMD	Reduction of group BMD	Mean value of BMD	statistic	P
Course of disease				12.159	**0.0004**
＜10years	17(81.0)	9(31.0)	0.16 ± 1.5		
≥ 10years	4(19.0)	20(69.0)	-1.33 ± 0.56		
Medication time				6.2256	**0.0120**
＜5years	14(66.7)	9(31.0)	0.057 ± 1.5		
≥ 5years	7(33.3)	20(69.0)	-1.07 ± 1.0		
VDR-TaqI				14.103	**0.0004**
TT		2(6.90)	-2.75 ± 0.073		
Tt	2(9.52)	16(55.2)	-1.37 ± 0.399		
tt	19(90.5)	11(37.9)	0.09 ± 1.42		
VDR-FokI				7.9479	**0.0120**
FF		6(20.7)	-1.35 ± 0.2		
Ff	21(100)	20(69.0)	-0.33 ± 1.4		
ff		3(10.3)	-2.03 ± 0.71		

Table 1: Baseline table of lumbar spine BMD in epilepsy patients.

Variable	Estimate	SE	WALD	P	OR(95%CI)
Gender (female as reference)	-0.0800	0.5778	0.0192	0.8899	0.923(0.297-2.865)
Age	0.0382	0.0200	3.6482	0.0561	1.039(0.999-1.081)
Course of disease (<10 as reference)	2.2453	0.6855	10.7285	0.0011	9.443(2.464-36.194)
Type of medication (liver enzyme inducer as reference)	0.4855	0.5947	0.6664	0.4143	1.625(0.507-5.213)
Duration of medication (<5 as reference)	1.4917	0.6127	5.9272	0.0149	4.444(1.337-14.769)
VDR-TaqI (Use tt as reference)	2.6479	0.8292	10.1963	0.0014	14.124(2.781-71.746)
VDR-FokI (Use ff as reference)	0.6076	0.7172	0.7176	0.3969	1.836(0.450-7.488)

Table 2: Univariate logistic regression analysis of Influencing factors of lumbar BMD reduction in epilepsy patients.

Multivariate stepwise logistic regression analysis of influencing factors of lumbar BMD reduction in epileptic patients.

With the reduction of lumbar BMD in epilepsy patients as the dependent variable, and the duration of disease, gender, age, type of medication, duration of medication VDR-TaqI and VDR-FoKI as the independent variables, multi-factor stepwise Logistic regression analysis was conducted. The results showed that: Age, medication duration, and VDR-TaqI were significantly correlated with reduced BMD in the lumbar spine of epilepsy patients, and T allele was the risk factor for decreased BMD in epilepsy patients (P<0.05, OR values were 1.112, 81.162, 279.56, respectively), as shown in Table 3.

Variable	β	SE	Wald	P	OR(95%CI)
Age	0.1065	0.0407	6.8460	0.0089	1.112(1.027-1.205)
VDR-TaqI （Use tt as reference）	5.6332	1.8366	9.4076	0.0022	279.56(7.641-10229)
Duration of medication (<5 as reference)	4.3964	1.5841	7.7022	0.0055	81.162(3.639-1810.413)

Table 3: Multivariate stepwise logistic regression analysis of factors affecting lumbar spine BMD reduction in epilepsy patients.

Baseline hip BMD in patients with epilepsy

The general and clinical data of the normal hip joint BMD group and the reduced hip joint BMD group were compared, and the disease course, VDR-TaqI and VDR-FokI between the two groups were statistically significant (P<0.05). The proportions of 10 years of disease duration, TaqI (TT), TaqI (Tt), FokI (FF), and FokI (ff) were higher in the BMD reduction group than in the BMD normal group. As shown in Table-4:2 cases of TaqI (TT), All were located in the BMD reduction group (7.41%); 18 Taq I (Tt), 3 patients (13%) in the BMD normal group, 15 (55.6%); Total of 30 cases of TaqI (tt), 20 (87%) in the BMD group, 10 cases (37%) in the reduction group; There were 6 cases of FokI (FF), Are located in the BMD reduction group (22.2%); 41 FokI (Ff), 22 (95.7%) in the BMD group, 19 patients (70.4%); 3 cases of FokI (ff), One (4.35), 2 cases in the reduced group (7.41%).

Variable	Normal group of BMD	Reduction group of BMD	Mean value of BMD	Statistic	P
Course of disease				8.1940	0.0042
< 10 years	17(73.9)	9(33.3)	0.11 ± 1.52		
≥ 10 years	6(26.1)	18(66.7)	-1.27 ± 0.65		
VDR-TaqI				13.097	0.0006
TT		2(7.41)	-2.6 ± 0.073		
Tt	3(13.0)	15(55.6)	-1.39 ± 0.49		
tt	20(87.0)	10(37.0)	0.09 ± 1.38		
VDR-FokI				**6.2730**	0.0210
FF		6(22.2)	-1.52 ± 0.322		
Ff	22(95.7)	19(70.4)	0.32 ± 1.40		
ff	1(4.35)	2(7.41)	-1.77 ± 1.1		

Table 4: Baseline table of hip BMD in patients with epilepsy.

Univariate logistic regression analysis of influencing factors for decreased hip BMD in epilepsy patients

With the reduction of hip joint BMD in epilepsy patients as the dependent variable, and age, gender, course of disease, type of medication, duration of medication, VDR-TaqI and VDR-FokI as the independent variables, univariate Logistic regression analysis was performed, and the results showed: VDR-TaqI and duration of disease were correlated with decreased hip BMD (P<0.05), as shown in Table 5.

Multivariate stepwise logistic regression analysis of influencing factors for hip BMD reduction

With the reduction of hip joint BMD in epilepsy patients as the dependent variable and gender, age, course of disease, type of medication, duration of medication, VDR-TaqI and VDR-FokI as the independent variables, multi-factor stepwise Logistic regression analysis was conducted. The results showed: VDR-TaqI and disease duration were significantly correlated with decreased hip BMD in epilepsy patients, and T allele was a risk factor for decreased hip BMD (P>0.05, OR 40.858, 25.363, respectively), as shown in Table 6.

Variable	Estimate	SE	WALD	P	OR(95%CI)
Gender (female as reference)	0.2877	0.5724	0.2526	0.6153	1.333(0.434-4.094)
Age	0.0188	0.0184	1.0414	0.3075	1.019(0.983-1.056)
Course of disease (< 10 as reference)	1.7346	0.6262	7.6725	0.0056	5.667(1.661-19.336)
Type of medication (liver enzyme inducer as reference)	0.0671	0.5796	0.0134	0.9078	1.069(0.343-3.330)
Duration of medication (<5 as reference)	1.1349	0.5909	3.6884	0.0548	3.111(0.977-9.906)
VDR-TaqI (Use tt a reference)	2.3378	0.7257	10.3779	0.0013	10.358(2.498-42.956)
VDR-FokI (Use ff as reference)	1.2218	0.8067	2.2939	0.1299	3.393(0.698-16.493)

Table 5: Univariate Logistic regression analysis of factors influencing hip bone mineral density reduction in patients with epilepsy.

Variable	β	SE	wald	P	OR(95%CI)
Course of disease (<10 as reference)	3.2333	1.1286	8.2068	0.0042	25.363(2.776-231.687)
VDR-TaqI (Use tt as reference)	3.7101	1.1801	9.8843	0.0017	40.858(4.044-412.817)

Table 6: Multivariate stepwise logistic regression analysis of the influencing factors of hip BMD reduction in patients with epilepsy.

Conclusion

The potential pathogenesis of reduced BMD in epilepsy patients may be related to VDR gene polymorphism: VDR-TAqi is associated with decreased BMD in hip and lumbar spine, and T allele is a risk factor for decreased BMD in epilepsy patients. Patients with TT genotype have the lowest BMD value, while those with tt genotype have the highest BMD value.

There was no significant association between VDR-FokI and BMD of hip and lumbar vertebrae in epileptic patients.

Discussion

Epilepsy is a common chronic nervous system disease, and correct oral medication is the main treatment. In recent years, long-term use of antiepileptic drugs (ASM) to reduce bone mineral density (BMD) and increase the risk of fracture has become a hot topic. However, the mechanism by which ASM affects bone health is unclear. So far, many hypotheses have been proposed, such as: Enzyme induced ASM (e.g., PHT, CBZ and PHB) induces the liver cytochrome P450 isoenzyme system responsible for vitamin D hydroxylation, resulting in increased hydroxylation and catabolism of vitamin D, resulting in vitamin D deficiency and reduced intestinal calcium absorption, which leads to secondary hyperparathyroidism and increased bone absorption to restore calcium homeostasis. This leads to lower BMD and eventually osteoporosis [13]. Carbonic anhydrase inhibitors ASM (such as topiramate) can damage renal tubules, thereby affecting bone metabolism [14]. CBZ and PHT can directly inhibit osteoblast proliferation within the therapeutic blood concentration range, and the reduction of proliferation may impair the formation of new bone [15]. However, the exact pathogenesis of decreased BMD in epileptic patients induced by ASM has not been determined. Based on the common vitamin D deficiency in epilepsy patients, it is considered that the underlying pathological mechanism may be related to the genetics of vitamin D receptor types [16].

The decrease of BMD in epilepsy patients is caused by a variety of factors, and the general situation of the individual will also have different degrees of influence on BMD, such as: gender, age, smoking, drinking, nutritional status and taking hormone drugs. In the course of this study, participants were always strictly screened, and the influence of other factors on BMD was excluded to the greatest extent, focusing on the relationship between the reduction of BMD and VDR-FokI and VDR-TaqI in epilepsy patients with long-term use of ASM.

This study focused on the correlation between VDR-TaqI and VDR-FokI and the decreased BMD in epilepsy patients. The patients' age, course of disease, type of medication, duration of medication, VDR-FokI and VDR-TaqI were taken as independent variables. With the reduction of hip and lumbar BMD in epilepsy patients as the dependent variable, a multi-factor stepwise Logistic regression analysis showed: The duration of the disease may be correlated with the decrease of hip BMD, age and time of taking medication may be correlated with the decrease of lumbar BMD, VDR-TaqI is correlated with the decrease of hip and lumbar BMD in epilepsy patients ($P<0.05$), and the T allele is a risk factor for the decrease of bone mass in epilepsy patients. The BMD of TaqI (Tt) was lower than that of TaqI (Tt) and TaqI (tt), and there was no correlation between VDR-FokI and the BMD of hip and lumbar vertebrae in epileptic patients ($P>0.05$).

VDR-TaqI is located in exon 9 and has been shown to affect the biological function of vitamin D. Seremak-Mrozikiewicz et al. found that VDR-TaqI was associated with BMD in postmenopausal women with osteoporosis in Poland, where the T allele had a higher risk of osteoporosis, especially in patients with TT genotype, whose BMD was lower than that of patients with Tt and tt genotype [17]. Rosa Giannina Castillo Avila system et al. The study found that VDR - TaqI and lumbar spine lesions and lumbar disc degeneration associated with increased risk [18]. In contrast to the above results, in a 2004 Turkish study, the authors found that in postmenopausal women with osteoporosis, individuals with the tt genotype had the highest BMD and lowest serum calcitonin levels [19]. However, in a meta-analysis of 14 studies consisting of 6,500 women with osteoporosis, no significant relationship was found between TaqI gene polymorphisms and fracture rates [20]. In this study, VDR-TaqI was associated with decreased BMD in epileptic patients: TaqI genotype was associated with decreased BMD in lumbar spine and hip joint of epileptic patients ($P<0.05$), the BMD value in VDR(TT) patients was the lowest, and the increase of T allele was a risk factor for decreased BMD (lumbar spine: OR=81.162; Hip joint: OR=40.858), which is consistent with Seremak-Mrozikiewicz et al.

VDR-FokI is located in exon 2 of the 5' coding region of the gene. The nucleotide sequence of the first codon changes from ATG to ACG resulting in 3 amino acids less than the size of the normal protein, making its affinity with 1,25 (OH) 2D3 low. Therefore, the genetic variation of FokI can affect the level of vitamin D. These genetic variants are associated with susceptibility to chronic diseases, such as type 2 diabetes, cancer, autoimmune diseases, cardiovascular diseases, rheumatoid arthritis, and metabolic bone diseases [21].A recent meta-analysis of the association between VDR-FokI and BMD showed that FokI gene polymorphism was associated with an increased risk of osteoporosis in Asian women, but not in Caucasians [22].The results of this study showed that there was no correlation between VDR-FokI and decreased BMD of lumbar spine and hip joint in epilepsy patients ($P>0.05$).It is speculated that the reasons for the differences with the above results may be related to the sample size and the influence of genetic (race) and environmental factors (region, light exposure, diet and calcium intake).It has been reported that the F allele of VDR-FokI is associated with *VDR* biological activity, improvement of vitamin D level and regulation of response to calcium supplements. The F allele has higher transfection activity than the f allele. Therefore, people with FokI-F allele may have higher vitamin D level and thus affect BMD [23-25]. The above results support that FF genotype has a high BMD value. Among the 50 patients enrolled in this study, 47 patients contained F alleles (FF, FF), and the mean BMD value of FF genotype was -1.35 ± 0.2, and 3 patients with ff genotype was -2.03 ± 0.71. That is, FF genotype has a higher BMD average than ff genotype, which is the same as the above conclusion.

This study has some limitations, such as a relatively small sample size and lack of vitamin D monitoring in enrolled patients. In the follow-up study, the above problems will be supplemented and improved, and the follow-up observation of patients and regular monitoring of BMD changes will be added, so as to further study the mechanism of vitamin D deficiency and increased fracture risk in patients with ASM and epilepsy.

Fragility fracture in patients with epilepsy is associated with a significant increase in mortality [6,7]. Therefore, for the treatment of patients with epilepsy, not only the control of epileptic seizures, but also the prevention, treatment and management of increased fracture susceptibility should be paid sufficient attention. Through the study on the correlation between VDR gene polymorphism and BMD reduction in patients, this study found that VDR-TaqI was correlated with BMD reduction in patients, which is expected to reveal its pathogenesis at the gene level. It is hoped that through continuous in-depth research, the risk factors causing bone

mass loss in patients can be found as early as possible, so that more patients with epilepsy can get rid of the risk of fracture disability as soon as possible, and can provide a new scientific basis for the development of prevention and treatment guidelines for bone strength loss in patients with epilepsy.

Conflict of interest and Funding

There was no funding for this study and no authors have conflicts of interest pertaining to the information in this manuscript.

References

1. Thurman, DJ, Beghi, E, Begley, et al. (2011) Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 52(7): 2-26.
2. Gu, L, Liang, B, Chen, Q, et al. (2013) Prevalence of epilepsy in the People's Republic of China: a systematic review. Epilepsy Res 105(1-2): 195-205.
3. Jiang, P, Zhu, WY, He, X, et al. (2015) Association between Vitamin D Receptor Gene Polymorphisms with Childhood Temporal Lobe Epilepsy. Int J Environ Res Public Health 12(11): 13913-13922.
4. Sözen T, Özışık L, Başaran NÇ (2017) An overview and management of osteoporosis. Eur J Rheumatol 4(1): 46-56.
5. Fortunato N (1996) Pathophysiology: The Biologic Basis for Disease in Adults and Children. AORN J 63(1): 294.
6. Whitney DG, Bell S, McNamara NA, et al. (2020) The mortality burden attributable to nontrauma fracture for privately insured adults with epilepsy. Epilepsia 61(4): 714-724.
7. Whitney DG, Kannikeswaran S, Whibley D (2020) Risk for respiratory and cardiovascular disease and mortality after non-trauma fracture and the mediating effects of respiratory and cardiovascular disease on mortality risk among adults with epilepsy. Epilepsy Res 166: 106411.
8. Shiek Ahmad B, Hill KD, O'Brien TJ, et al. (2012) Falls and fractures in patients chronically treated with antiepileptic drugs. Neurology 79(2): 145-151.
9. Elmazny A, Amer H, Rashed L, et al. (2020) Vitamin D status of untreated children and adolescent Egyptian patients with genetic generalized epilepsy: A case-control study. Epilepsy Behav 103(Pt A): 106840.
10. Morrison NA, Qi JC, Tokita A, et al. (1994) Prediction of bone density from vitamin D receptor alleles. Nature 367 (6460): 284-287.
11. Eisman JA (2001) Pharmacogenetics of the vitamin D receptor and osteoporosis. Drug Metab Dispos 29(4 Pt 2): 505-12.
12. Lambrinoudaki I, Kaparos G, Armeni E, et al. (2011) BsmI vitamin D receptor's polymorphism and bone mineral density in men and premenopausal women on long-term antiepileptic therapy. Eur J Neurol 18(1): 93-98.
13. Miziak B, Chrościńska-Krawczyk M, Czuczwar SJ (2019) An update on the problem of osteoporosis in people with epilepsy taking antiepileptic drugs. Expert Opin Drug Saf 18(8): 679-689.
14. Nakken KO, Taubøll E (2010) Bone loss associated with use of antiepileptic drugs. Expert Opin Drug Saf 9(4): 561-571.
15. Petty SJ, Milligan CJ, Todaro M, et al. (2016) The antiepileptic medications carbamazepine and phenytoin inhibit native sodium currents in murine osteoblasts. Epilepsia 57(9): 1398-1405.
16. Dussault PM, Lazzari AA (2017) Epilepsy and osteoporosis risk. Curr Opin Endocrinol Diabetes Obes 24(6): 395-401.
17. Seremak-Mrozikiewicz A, Drews K, Mrozikiewicz PM, et al. (2009) Correlation of vitamin D receptor gene (VDR) polymorphism with osteoporotic changes in Polish postmenopausal women. Neuro Endocrinol Lett 30(4): 540-546.
18. Castillo-Avila RG, González-Castro TB, Tovilla-Zárate CA, et al. (2021) The role of TaqI, ApaI and BsmI polymorphisms of VDR gene in lumbar spine pathologies: systematic review and meta-analysis. Eur Spine J 30(7): 2049-2059.
19. Duman BS, Tanakol R, Erensoy N, et al. (2014) Vitamin D receptor alleles, bone mineral density and turnover in postmenopausal osteoporotic and healthy women. Med Princ Pract 13(5): 260-266.
20. Shen H, Xie J, Lu H (2014) Vitamin D receptor gene and risk of fracture in postmenopausal women: a meta-analysis. Climacteric 17(4): 319-24.
21. Beysel S, Eyerci N, Pinarli FA, et al. (2018) VDR gene FokI polymorphism as a poor prognostic factor for papillary thyroid cancer. Tumour Biol 40(11): 1010428318811766.
22. Zhang L, Yin X, Wang J, et al. (2018) Associations between VDR Gene Polymorphisms and Osteoporosis Risk and Bone Mineral Density in Postmenopausal Women: A systematic review and Meta-Analysis. Sci Rep 8(1): 981.
23. Emerah AA, El-Shal AS (2013) Role of vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D level in Egyptian female patients with systemic lupus erythematosus. Mol Biol Rep 40(11): 6151-6162.
24. Lee YH, Kim JH, Song GG. (2014) Vitamin D receptor polymorphisms and susceptibility to Parkinson's disease and Alzheimer's disease: a meta-analysis. Neurol Sci 35(12): 1947-1953.

***Corresponding author:** Yan-mei Zhu, Department of Epilepsy and Sleep Disorder, Second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, 150086, Harbin, China; Email: zymtg1111@163.com

Received date: August 28, 2023; **Accepted date:** October 23, 2023; **Published date:** October 31, 2023

Citation: Chen X, Zhong W, Chen Y, He J, Gou H, Zhu Y (2023) Relationship Between BMD Reduction and VDR Gene Polymorphism in Patients with Epilepsy. *Int J Neuro Sci Res* 3(1): 107.