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Original Research Article

Vitamin D receptor gene polymorphism in patients with aseptic necrosis of the femoral head: a comparative cross-sectional study

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ABSTRACT

Background: This study explored the correlation of the Met1Thr (rs2228570) polymorphism of the vitamin D receptor (VDR) gene with aseptic necrosis of the femoral head (ANFH).
Methods: This comparative cross-sectional study consisted of 74 patients divided into group 1 of 44 patients with ANFH and group 2 of 30 patients with hip osteoarthritis stage 3 by Kellgren-Lawrence classification. The VDR genotyping was conducted on venous blood samples. Serum vitamin D_3 and osteocalcin were quantified via enzyme immunoassays. Statistical analyses consisted of χ^2 tests for genotype distribution and Mann-Whitney U-tests for biochemical parameters, considering for non-normal distributions.
Results: There were no statical significant differences were observed in Met1Thr genotype distribution between ANFH and osteoarthritis groups (χ^2=2.081; p=0.353). The carriers of the G (Thr) allele revealed a non-significant pattern toward elevated ANFH risk (OR=2.16; 95% CI 0.74-6.31). Both groups showed severe vitamin D deficiency (median 25(OH)D<30 ng/ml) and significantly reduced osteocalcin levels, reflecting reduced bone turnover rate. No statistically significant differences in Vitamin D_3 or osteocalcin levels were noted between groups.
Conclusions: Severe vitamin D deficiency and suppressed osteoblastic activity distinguished both ANFH and osteoarthritis. Although the Met1Thr VDR polymorphism was more common in ANFH patients, its connection with disease risk was not statistically significant. These findings suggest vitamin D deficiency as a key risk factor and highlight further research on VDR polymorphisms in larger cohorts.
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Keywords: Vitamin D receptor gene, Polymorphism, Aseptic necrosis, Femoral head, Vitamin D deficiency, Hip osteoarthritis

INTRODUCTION

Aseptic necrosis of the femoral head (ANFH) is a degenerative vascular condition of bone resulting from compromised blood flow to the proximal femur, consequently resulting in osteonecrosis, collapse of bone structural integrity, subchondral fractures, and degradation of the articular surface, leading to severe arthritis.[1,2] This condition primarily affects adults aged 30-50 years, particularly those who use corticosteroids, consume alcohol, or experience trauma.[3] In the US, the annual prevalence is estimated to be 20,000-30,000 cases, with a significant increase in prevalence rates in Asian countries. ANFH affects individuals aged 20-60 years, with a

significantly higher incidence in males (1.02%) than in females (0.51%). The bilateral involvement of ANFH is approximately 37% of all cases recorded globally. This condition is a key factor for hip pain and joint replacement surgery.[4] The underlying cause of ANFH is primarily due to bone ischemia resulted from occlusion of vessels or vascular damage leading to poor perfusion, elevated intraosseous pressure and hypertrophy of lipocytes eventually causing the vascular collapse of femoral head. Etiologically, ANFH is subdivided into traumatic causes, such as hip dislocation, femoral neck fractures, and acetabular fractures damaging the retinacular vessels; atraumatic causes, such as corticosteroid usage, alcohol abuse, coagulopathies, metabolic conditions, and environmental factors (Caisson disease); and idiopathic causes, accounting for approximately 30% of cases recorded worldwide.[5]

Genetic factors play a major role in the development of aseptic necrosis of the femoral head, especially in cases without a traumatic etiology. In sporadic cases, certain genetic polymorphisms, particularly those in genes that regulate coagulation, bone metabolism, angiogenesis, and steroid or alcohol abuse, are strong indicators of elevated risk.[6]

The main genetic aspects include familial aggregation (in COL2A1 gene, affecting type II collagen causing structural issues of hip), coagulation and thrombosis (specific polymorphism of 4G allele in the PAL-1 gene found osteonecrosis of femoral head patients), bone turnover and metabolism (polymorphism in RANK, RANKL, OPG, BMP), metabolism factors (various genetic variations for alcohol metabolism such as ADH2, ALDH2 and angiogenesis such as VEGFC, IGFBP3, ACE) and environmental risk factors (steroids and alcohol).[7] The vitamin D receptor (VDR) gene controls transcription regulators that facilitates the key biological actions of active vitamin D3 (calcitriol). The VDR gene is responsible for maintaining calcium/phosphate homeostasis, cell differentiation, and immune responses.[8]

The structure of the VDR gene comprises several protein domains, such as an N-terminal A/B domain, DNA-binding domain (DBD), hinge domain, and ligand-binding domain (LBD), which are responsible for the proper functioning of the VDR.[9] The most frequent VDR gene polymorphisms are FokI(rs2228570), BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236) and Cdx2 (rs11568820).[10] Furthermore, the major role of VDR gene in bone metabolism and skeletal disorders is to control osteoporosis risk, rate of bone turnover and fractures, secondary hyperparathyroidism, rickets and the treatment response of vitamin D.[11,12]

In addition, the literature on VDR gene polymorphisms and aseptic necrosis (osteonecrosis) is limited by the number of studies conducted in small populations, limited data on specific VDR gene polymorphisms, lack of evidence for an interaction with environmental factors, need for functional studies, and ethnic and genetic variability. The potential clinical implications of VDR genotyping are necessary for risk stratification, early intervention, personalized therapy, and as a diagnostic tool to identify high-risk patients for bone fragility associated with vascular issues. Furthermore, this study explored the association of VDR gene polymorphisms in patients with aseptic necrosis of the femoral head to fill the current limitation in the literature in this field of orthopedics. In conclusion, this study aims to assess the levels of total vitamin D and osteocalcin in the blood of patients with aseptic necrosis of the femoral head and to investigate the polymorphism of the VDR gene (rs2228570, C/T) to identify any genetic predisposition to the development of this condition.

METHODS

This comparative analysis was conducted at the Department of Traumatology, Orthopedics, and Military Field Surgery at the Grodno City Clinical Hospital for Emergency Medical Care during the period 1st of June 2024 to 31st of March 2025.

Table 1: Comparative analysis of patient groups by key parameters.

Parameter	Group 1 (ANGBK n=44)	Group 2 (hip osteoarthritis, n=30)	Comment
Average age (years)	53.9 (from 28 to 84)	61.3 (from 26 to 74)	Patients with coxarthrosis were, on average, 7.4 years older.
Gender (M/F)	32 men (72.7%), 12 women (27.3%)	17 men (56.7%), 13 women (43.3%)	In the ANGBK group, the proportion of men was 16% higher.
COVID-19 indication	7 patients (15.9%)	0 patients (0%)	An association with COVID-19 was observed only in the necrotic group.
Bilateral defeat	30 patients (68.2%)	28 patients (93.3%)	Bilateral processes are more common in coxarthrosis.
Presence of coxarthrosis	Seven patients (15.9%) had it as a result of ANFH.	Thirty patients (100%) had an underlying disease.	Coxarthrosis is a natural stage of ANFH in some patients.

The patients were divided into group 1 (aseptic necrosis of the femoral head, ANFH; 44 patients) and group 2 (hip osteoarthritis; 30 patients). The inclusion criteria for this study were patients with a diagnosis of M87.0 (unilateral

or bilateral aseptic necrosis of the femoral head), M16.0, and M16.1 (unilateral or bilateral stage 3 hip osteoarthritis by Kellgren-Lawrence), and patients who provided informed consent. The exclusion criteria were patients without written informed consent, patients with other degenerative joint diseases excluding the hip joint, patients with acute infection or inflammatory disease, patients with malignant diseases, and patients with diagnosed severe renal or hepatic failure. A comparative analysis of the patient groups based on key parameters is presented in Table 1. The group of patients with aseptic necrosis of the femoral head consisted mainly of men (72.7%), with a mean age of 54 years. Of these patients, 15.9% had COVID-19. In 68.2% of the patients, the disease affected both hip joints. Among the comorbidities, in addition to age-related hypertension and coronary heart disease, obesity, gout, type 2 diabetes, and various liver pathologies are common.

The group of patients with hip osteoarthritis comprised older individuals with an average age of 61 years and a nearly equal ratio of men (56.7%) to women (43.3%). Joint damage in this group was predominantly bilateral (in 93.3% of cases), and five patients had already undergone joint replacement. Comorbidities reflected the overall degenerative background: systemic atherosclerosis (manifested as coronary artery disease and damage to other arteries), hypertension, and hypercholesterolemia were common.

Based on informed consent, after analyzing radiographs and CT data, venous blood was collected, centrifuged at 3000 rpm for 10 minutes, and the resulting plasma was divided into two test tubes for further biochemical testing to determine the level of total vitamin D and osteocalcin. Blood samples were also collected for genetic testing.

Quantitative determination of serum osteocalcin levels was performed using the Human enzyme immunoassay kit. OC / BGP (Osteocalcin) ELISA Kit Cat. No. EN3468. At the beginning of the analysis, a series of dilutions of standards of a given concentration were prepared to construct a calibration curve. Blood serum samples were also prepared. Blood samples were diluted 1:1 with sample dilution buffer in an additional plate. Prepared standards and diluted blood serum samples were added to the wells of a plate containing immobilized osteocalcin antibodies. The plate was placed in a thermoshaker. BIOSAN PST - 60 HL for incubation at 37º C. Then the plate was washed on a microplate washer APW-200. Next, the working solution of biotin antibodies was added to the wells of the plate, followed by incubation in a thermoshaker at 37°C. After washing, the working solution of HRP-streptavidin-conjugate was added to the wells of the plate and incubated at 37°C. This was followed by incubation at 37°C, followed by washing. Tetramethylbenzidine (TMB) solution was then added, after which a blue color developed during incubation at 37°C. The color reaction was stopped by adding the stop solution. The solution turned yellow. The intensity of the color was proportional to the amount of osteocalcin in the blood samples.

Quantitative determination of osteocalcin levels in the blood serum with the construction of a calibration curve was carried out using a microplate photometer. HiPo MPP -96. The obtained data were then processed, and the average osteocalcin levels were calculated.

Vitamin levels were also quantified. Vitamin D in blood serum was measured using the Human Enzyme Immunoassay kit VD (Vitamin D) ELISA Kit (Cat. No. E U 2541). The determination method was the same as that used for determining the osteocalcin level; however, undiluted blood serum was used in the study.

RESULTS

Statistical analysis of 25(OH)D concentration in patients with hip osteoarthritis and aseptic necrosis of the femoral head

A comparative analysis of serum 25(OH)D levels was conducted in patients with hip osteoarthritis (n=28) and aseptic necrosis of the femoral head (ANFH, n=41). During data preprocessing, extremely high values were identified in both groups, reaching 69.46 ng/ml and 72.16 ng/ml, respectively, requiring additional analysis to account for potential outliers.

Table 2: Observed frequencies.

Group	AA (Met/Met)	AG (Met/Thr)	GG (Thr/Thr)	Total
ANGBK	9	22	11	42
Coxarthrosis	10	12	5	27
Total	19	34	16	69

Descriptive statistics revealed severe vitamin D deficiency (concentration <30 ng/ml) in both study groups. In the hip osteoarthritis group, the mean concentration was 8.66 ng/ml (SD=13.32), the median was 3.79 ng/ml, with an interquartile range of 2.97-8.72 ng/ml. In the ANFH group, the mean value was 5.66 ng/ml (SD=10.52), the median was 2.82 ng/ml, and the interquartile range was 1.71-5.33 ng/ml. The significant difference between the mean and median, as well as the high standard deviation values, indicates a strong right-sided asymmetry of the distribution in both cohorts. Statistical testing of the distribution using the Shapiro-Wilk test confirmed a significant deviation from normality ($p<0.001$ for both groups). Levene's test for homogeneity of variances showed no statistically significant differences in their magnitude ($p=0.265$). Given the non-normal nature of the

distribution, the non-parametric Mann-Whitney U-test was used to compare the groups. A comparison of the groups revealed no statistically significant differences in 25(OH)D levels (U=465.0, p=0.119). To assess the stability of the results, an additional analysis was performed after excluding extreme values (>60 ng/ml). After excluding outliers, the mean values were 5.31 ng/ml for coxarthrosis (n=27) and 4.45 ng/ml for ANFH (n=40). Repeated application of the Mann-Whitney test also revealed no significant differences (U=485.0, p=0.282). In conclusion, patients with both hip osteoarthritis and ANFH exhibited severe vitamin D deficiency. No statistically significant differences in 25(OH)D concentrations were found between the compared groups. The observed difference in mean values (8.66 vs. 5.66 ng/ml) is explained by the presence of extreme values and the asymmetry of the data distribution, rather than by systematic differences between the pathologies.

Table 3: Expected frequencies.

Group	AA	AG	GG
ANGBK	11.565	20.696	9.739
Coxarthrosis	7.435	13.304	6.261

Statistical analysis of serum osteocalcin levels in patients with hip osteoarthritis and aseptic necrosis of the femoral head

An analysis of the data was conducted, including 42 observations in the group of patients with aseptic necrosis of the femoral head (ANFH) and 27 observations in the group with coxarthrosis. Extreme values were identified in the raw data during the preprocessing stage. In the coxarthrosis group, a value of 380.66 ng/ml was recorded, whereas in the ANFH group, values of 95.90 ng/ml, 34.93 ng/ml, and 25.57 ng/ml were recorded.

A descriptive analysis of the baseline data showed an important difference between the arithmetic mean and median in both groups, reflecting a highly asymmetric distribution of the parameters. Thus, in the ANFH group, the average osteocalcin level was 4.67 ng/ml with a median of 1.31 ng/ml and standard deviation of 14.82 ng/ml. In the coxarthrosis group, the average value was 15.71 ng/ml with a median of 0.85 ng/ml and a standard deviation of 73.04 ng/ml. The interquartile range for the ANFH group ranged from 0.09-2.02 ng/ml, and for the coxarthrosis group, from 0.08-1.97 ng/ml.

After excluding extreme outliers (values >50 ng/ml), which resulted in the removal of three observations from the ANFH group and one from the coxarthrosis group, adjusted values were obtained. In the ANFH group (n=39), the mean osteocalcin level decreased to 1.56 ng/ml with a median of 1.11 ng/ml and a standard deviation of 1.41 ng/ml. In the coxarthrosis group (n=26), the mean value was 1.37 ng/ml with a median of 0.82 ng/ml and a standard deviation of 1.62 ng/ml. Testing the distribution for normality using the Shapiro-Wilk test showed that both the original data ($p<0.001$ for both groups) and those after removing outliers ($p<0.001$ for both groups) significantly deviated from a normal distribution. Therefore, the nonparametric Mann-Whitney test was used to compare the groups. No statistically significant differences were found between the groups in the analysis of the original data (U=512.0, p=0.298) or after removing outliers (U=454.5, p=0.294).

The clinical interpretation of the results was performed considering the reference interval for osteocalcin (11-45 ng/ml). Median values in both groups (1.31 ng/ml for ANFH and 0.85 ng/ml for coxarthrosis) were 8-13 times lower than the lower limit of normal, indicating a significant decrease in bone formation characteristic of bone hypometabolism.

Thus, the study revealed no statistically significant differences in serum osteocalcin levels between patients with ANFH and coxarthrosis. The main clinical finding was the similar and profound suppression of osteoblastic activity in both conditions, indicating severe bone metabolism disorders.

Statistical analysis of the distribution of met1Thr (rs2228570) genotypes of the VDR gene

The null hypothesis (H_0) of the genotype distribution (AA, AG, GG) of the Met1Thr polymorphism of the VDR gene does not differ between the ANFH and coxarthrosis groups. The alternative hypothesis (H_1) is that the distribution does differ. Therefore, the significance level was set at $\alpha=0.05$.

Table 4: Pearson's χ^2 criterion.

Cell (group/genotype)	$(O_{ij} - E_{ij})^2 / E_{ij}$
ANGBK/AA	0.569
ANGBK/AG	0.082
ANGBK/GG	0.163
Coxarthrosis/AA	0.885
Coxarthrosis/AG	0.128
Coxarthrosis/GG	0.254
Sum (χ^2)	2.081

The conclusion based on the χ^2 criterion ($\chi^2=2.081$; df=2; $p=0.353$) revealed that the differences in genotype distribution among the groups were not statistically significant ($p>0.05$). Therefore, this observation does not reject the null hypothesis.

No statistically significant association was observed between the Met1Thr polymorphism (rs2228570) of the VDR gene and the development of ANFH compared with coxarthrosis in this sample (n=69) (p=0.353).

A trend was observed in the dominant model; carriage of the G (Thr) allele was associated with a 2.16-fold

increased risk of ANFH (OR=2.16); however, the 95% confidence interval (0.74;6.31) included one, indicating statistical ambiguity of this effect.

Table 5 (A): Analysis in genetic models (odds ratio, OR): Dominant model for the G (Thr) allele.

Group	AG+GG (G-carriers)	AA	Total
ANGBK	33	9	42
Coxarthrosis	17	10	27

Table 5 (B): Analysis in genetic models (odds ratio, OR): Allelic model.

Group	Allele G	Allele A	Total
ANGBK	44	40	84
Coxarthrosis	22	32	54

DISCUSSION

This study explored the correlation between the Met1Thr (rs2228570) polymorphism of the vitamin D receptor (VDR) gene and aseptic necrosis of the femoral head (ANFH), differentiating patients with ANFH and coxarthrosis. The results indicated no statistically significant difference in genotype distribution among the groups, with a χ^2 value of 2.081 (p=0.353). Although a pattern was observed in the dominant model, in which carriers of the G (Thr) allele had a 2.16-fold increased risk of ANFH (OR=2.16), the confidence interval crossed the null value, reflecting statistical uncertainty. Additionally, both groups exhibited severe vitamin D deficiency and significantly reduced serum osteocalcin levels, indicating significant bone metabolism impairment that is common to both conditions.

These findings partially mirror previous studies linking VDR polymorphisms to skeletal disorders, such as osteoporosis and fractures, wherein VDR variants affect bone turnover and calcium homeostasis.[13] However, the limited evidence on VDR polymorphisms, especially in ANFH, and the lack of significant correlation in this study emphasize the multigenic architecture of this vascular bone disease.[14] Potential mechanisms by which VDR variants influence ANFH, such as modulation of bone remodeling, regulation of immune responses, and vascular function, are important in bone ischemia and repair processes.[15] The detected vitamin D deficiency and suppressed osteoblastic activity further validate the role of disrupted bone metabolism in ANFH pathogenesis.[16,17]

The identification of VDR gene polymorphisms as risk factors for ANFH could improve early risk stratification and individual management strategies. However, in the absence of statistically significant associations in this study, the clinical application of VDR genotyping remains limited. The severe vitamin D deficiency observed in patients with both ANFH and coxarthrosis highlights the significance of observing and correcting vitamin D status as part of multidisciplinary care. Precision medicine concentrating on vitamin D supplementation and bone turnover regulation shows potential yet require further validation. Interpreting genetic associations in clinical practice faces challenges, such as genetic heterogeneity, ecological relationships, and the multifactorial nature of ANFH.

Strengths and limitations of the study

This study merits from a comparative design including well-defined groups with ANFH and coxarthrosis, allowing a direct assessment of VDR polymorphism distribution and associated biochemical markers. The utility of standardized biochemical assays for vitamin D and osteocalcin levels reinforces the authenticity of metabolic findings. However, the small sample size (n=69) restricts statistical power, especially for identifying modest genetic effects. The cross-sectional design prevents causal inference, and influencing factors such as environmental factors, other genetic variants, and comorbidities were not rigorously controlled. In addition, the ethnic and genetic background of the study population may restrict generalizability.

CONCLUSION

This study revealed a shared adverse metabolic profile in patients with hip pathology, characterized by severe vitamin D deficiency and a significant reduction in osteocalcin levels, reflecting impaired bone formation and elevated skeletal vulnerability. The G (Thr) allele of the vitamin D receptor (VDR) gene was more common in aseptic necrosis of the femoral head (ANFH) patients, correlated with 2.16-fold increased odds of disease, highlighting the modulatory role amongst vitamin D deficiency. Clinically, ANFH patients were younger, predominantly male, and some arrived prior COVID-19 infection, while bilateral joint involvement was more frequent in coxarthrosis. These findings emphasize vitamin D deficiency as a major risk factor common to both conditions and indicates the Met1Thr VDR polymorphism as a potential genetic contributor to ANFH, requiring validation in larger cohorts. Routine screening and correction of vitamin D status, observing bone metabolism via osteocalcin, and genetic analyses including gene-ecological relationships are recommended. Individualized prevention therapies, particularly for patients with VDR variants undergoing corticosteroid therapy, should be developed. Furthermore, the results support the complex etiology of ANFH caused by genetic predisposition and metabolic abnormalities. Although genetic associations were not statistically significant, observed patterns are clinically significant and justify further investigation.

Recommendations

Larger studies such as multicenter studies between diverse populations are necessary to reproduce these findings and

validate the major role of VDR polymorphisms in ANFH vulnerability. Functional studies exploring the specificity of VDR gene variants affecting receptor activity and the function of bone cells and vascular integrity will elaborate the underlying mechanisms.

Translating genetic information with environmental interactions, status of vitamin D, and other biomarkers could improve the risk prediction models of this condition. Furthermore, longitudinal studies investigating the effect of vitamin D supplementation and targeted treatments on progression of the disease in genetically defined cohorts would develop multidisciplinary care for these patients.

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