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THE ROLE OF BSMI AND APAI POLYMORPHISMS OF THE VITAMIN D RECEPTOR GENE IN THE DEVELOPMENT OF LOW BONE MINERAL DENSITY IN ADULTS. LITERATURE REVIEW

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Abstract

Background. Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mineral density (BMD), which leads to an increased risk of fractures and greater bone fragility [1]. The global prevalence of osteoporosis is estimated to be 18.3%. Gender and genetics are non-modifiable risk factors for osteoporosis, whereas other factors (modifiable ones) can be influenced, such as diet, physical activity, and lifestyle. Vitamin D plays a crucial role in bone metabolism and is essential for the prevention of osteoporosis (OP). In recent years, numerous studies have been conducted to explore the correlation between VDR gene variants and osteoporosis risk, suggesting the presence of ethnic differences in the genetic association with osteoporosis. However, there is still no definitive evidence confirming their impact in the studies conducted so far.

The aim was of this review is to examine the available literature on the role of vitamin D and the association of BsmI and ApaI polymorphisms in the development of low mineral density.

Search Strategy: A systematic search was conducted in the electronic databases PubMed and Google Scholar using the following keywords: “osteoporosis,” “BsmI,” “ApaI,” “VDR gene,” “bone mineral density, and “vitamin D.” The search was limited to English-language studies published between 2014 and 2024. A total of 24 sources were reviewed. The article selection for this review was conducted by the authors, who identified relevant studies and excluded those that did not meet the inclusion criteria.

Conclusion. Although some studies on various populations have identified an association between several VDR gene polymorphisms and bone mineral density (BMD), many questions in this area remain unresolved. Research on VDR gene polymorphisms has shown that their impact on low BMD can yield different results across populations.

Keywords: *osteoporosis, BsmI, ApaI, VDR gene, bone mineral density, vitamin D.*

Резюме

РОЛЬ ПОЛИМОРФИЗМОВ BSMI, APAI ГЕНА РЕЦЕПТОРА ВИТАМИНА D В РАЗВИТИИ НИЗКОЙ МИНЕРАЛЬНОЙ ПЛОТНОСТИ КОСТНОЙ ТКАНИ У ВЗРОСЛЫХ. ОБЗОР ЛИТЕРАТУРЫ.

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Актуальность. Остеопороз является системным заболеванием скелета, характеризующееся снижением минеральной плотности кости (МПК), которое приводит к риску переломов и повышенной хрупкости костей.

Глобальная распространенность остеопороза оценивается в 18,3%. Пол или генетика являются немодифицирующими факторами риска остеопороза, в то время как другие факторы (модифицирующие) могут быть изменены, например диета, физическая активность и образ жизни. Вклад генетической изменчивости VDR в патогенез ОП все еще неясен и полон пробелов. В последние годы было проведено множество исследований для изучения корреляции между вариантами гена VDR и риском остеопороза, что предполагает наличие этнических различий в генетической ассоциации с остеопорозом. Но до сих пор нет четких доказательств их влияния в проведенных исследованиях.

Целью обзора является изучение литературных данных о роли витамина D и связи полиморфизмов BsmI, ApaI в развитии снижения МПК.

Стратегия поиска: Проведен систематический поиск в электронных базах PubMed, Google Academy, по ключевым словам, как «остеопороз», «BsmI», «ApaI», «ген VDR», «минеральная плотность кости», «витамин Д». Этот поиск был ограничен англоязычными исследованиями, опубликованными с 2014 по 2024 гг. Всего изучено 24 источника. Поиск статей для обзора осуществлялся авторами, которые отбирали подходящие статьи и исключали все статьи, не соответствующие требованиям.

Выводы. Несмотря на то, что в некоторых исследованиях на различных популяциях была выявлена связь нескольких полиморфизмов гена VDR с МПК, многие вопросы в этой области до конца не изучены. Изучение полиморфизмов гена VDR показало, что в разных популяциях влияние полиморфизмов на низкую МПК может иметь разные результаты.

Ключевые слова: *остеопороз, BsmI, ApaI, ген VDR, минеральная плотность кости, витамин D.*

Түйіндеме

D ДӘРУМЕН РЕЦЕПТОРЫ BSMI, APAI ПОЛИМОРФИЗМДЕРІНІҢ ЕРЕСЕК АДАМДАРДАҒЫ СҮЙЕК ТІНІНІҢ МИНЕРАЛЬДЫ ТЫҒЫЗДЫҒЫНЫҢ ТӨМЕНДЕУІНЕ ӘСЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Остеопороз сыну қауіптілігі мен сүйектің жоғары сынғыштығына әкелетін, сүйектің минеральды тығыздығының төмендеуімен сипатталатын қаңқаның жүйелі ауруы болып табылады. Остеопороздың жоғары таралымы 18,3% құрайды. Жыныс пен генетика остеопороздың модифицирленбеген (өзгермейтін) қауіп факторларына жатқызылады, сонымен қатар басқа факторлар модифицирленген, яғни өзгермелі факторларға жатқызылады, мысалы, емдәм, физикалық белсенділік және өмір сүру салты. VDR генетикалық өзгергіштігінің ОП патогенезіндегі маңызы әлі толық зерттелмеген. Соңғы жылдары VDR гені мен остеопороз даму қаупі арасындағы байланысты анықтау үшін көптеген зерттеулер жүргізілді, ол остеопорозбен генетикалық байланыста этникалық айырмашылықтың болуын болжамдайды. Бірақ әлі де өткізілген зерттеулер нәтижелерінде оның әсері бойынша толық дәлел жоқ.

Шолудың мақсаты бұл D дәрумені маңыздылығы мен сүйектің минеральды тығыздығы төмендеуіне BsmI, ApaI полиморфизмдерінің байланысын анықтау.

Әдістері. Іздеу стратегиясы: PubMed, Google Academy электронды базаларында "остеопороз", "BsmI", "ApaI", "VDR гені", "сүйектің минералды тығыздығы", "D дәрумені" түйін сөздер бойынша жүйелі іздеу жүргізілді. Бұл іздеу 2014 жылдан 2024 жылға дейін жарияланған ағылшын тіліндегі зерттеулермен шектелді.Барлығы 24 мақалаға шолу жасалынды. Шолу жүргізу барысында авторлар талаптарға сай келетін мақалаларды жинақтап, сай келмейтін мақалаларды алып тастады.

Қорытынды. Әртүрлі популяцияларда жүргізілген зерттеу нәтижелерінде VDR генінің сүйектің минеральды тығыздығына әсері анықталғанымен, бұл салада туындаған көптеген сұрақтар соңына дейін зерттелмеген. VDR гені полиморфизмдерін зерттеу әртүрлі популяцияларда сүйектің минеральды тығыздығына әсерін анықтау әр алуан нәтиже көрсетуі мүмкін екені дәлелденген.

Түйін сөздер: *остеопороз, BSMI, ApaI, VDR гені, сүйектің минералды тығыздығы, D дәрумені.*

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Madiyeva M., Kaskabayeva A., Kultumanova N., Bersimbekova G., Kanapiyanova G., Sarmanova Zh., Sabyrkyzy M. The Role of BsmI and ApaI Polymorphisms of the Vitamin D Receptor Gene in the Development of Low Bone Mineral Density in Adults. Literature Review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2024. Vol.26 (6), pp. 115-121. *doi 10.34689/SH.2024.26.6.014*

Мадиева М., Каскабаева А., Культуманова Н., Берсимбекова Г., Канапиянова Г., Сарманова Ж., Сабыркызы М. Роль полиморфизмов BsmI, ApaI гена рецептора витамина D в развитии низкой минеральной плотности костной ткани у взрослых. Обзор литературы // Наука и Здравоохранение. 2024. Т.26 (6). С. 115-121. *doi 10.34689/SH.2024.26.6.014*

Мадиева М., Каскабаева А., Культуманова Н., Берсимбекова Г., Канапиянова Г., Сарманова Ж., Сабыркызы М. D дәрумен рецепторы BsmI, ApaI полиморфизмдерінің ересек адамдардағы сүйек тінінің минеральды тығыздығының төмендеуіне әсері. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2024. Т.26 (6). Б. 115-121. *doi 10.34689/SH.2024.26.6.014*

Introduction

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mineral density (BMD), which leads to an increased risk of fractures and greater bone fragility [11]. The global prevalence of osteoporosis is estimated to be 18.3%. The World Health Organization (WHO) has projected that by 2025, there will be approximately three million hip fractures annually due to osteoporosis [21]. Assessing genetic predisposition to osteoporosis is particularly important because the disease is asymptomatic; in most cases, the first clinical manifestation is a low-energy fracture. Additionally, the number of elderly individuals at high risk of fractures due to bone fragility is increasing [12]. Since the population of most Asian countries is aging, the frequency of fractures caused by osteoporosis is also rising in these regions. Forecasts suggest that by 2050, more than 50% of hip fractures will occur in Asian countries [16]. Gender and genetics are non-modifiable risk factors for osteoporosis, whereas other factors (modifiable ones) can be influenced, such as diet, physical activity, and lifestyle. Vitamin D plays a crucial role in bone metabolism and is essential for the prevention of osteoporosis (OP). One of its primary functions is regulating calcium (Ca^{2+}) absorption efficiency [5]. The biological activity of vitamin D is mediated through its receptor, which is encoded by the VDR gene [1]. The vitamin D receptor (VDR) has been proposed and continues to be studied by researchers worldwide as a candidate gene for osteoporosis [23]. However, the contribution of VDR genetic variability to OP pathogenesis remains unclear and full of gaps. Variations in literature findings may be explained by several factors, including differences in allele distribution among ethnic groups, which are critical for determining disease susceptibility [10]. The potential influence of the vitamin D receptor (VDR) on bone mineral homeostasis has attracted significant scientific interest due to its essential role in cellular metabolism and bone structure remodeling [2]. In recent years, numerous studies have been conducted to explore the correlation between VDR gene variants and osteoporosis risk, suggesting the presence of ethnic differences in the genetic association with osteoporosis. However, there is still no definitive evidence confirming their impact in the studies conducted so far [13,24].

The aim was of this review is to examine the available literature on the role of vitamin D and the association of BsmI and ApaI polymorphisms in the development of decreased BMD.

Keywords: osteoporosis; BsmI; ApaI; VDR gene; bone mineral density; vitamin D.

Methods. Search Strategy: A systematic search was conducted in the electronic databases PubMed and Google Scholar using the following keywords: «osteoporosis», «BsmI», «ApaI», «VDR gene», «bone mineral density», and «vitamin D». The search was limited to English-language studies published between 2014 and 2024. A total of 23 sources were reviewed.

Inclusion Criteria: Studies were included in the review based on the following criteria: (1) data on the global prevalence of osteoporosis, (2) data on risk factors for osteoporosis development in adults, (3) studies published in English, (4) research on the role of vitamin D receptor gene polymorphisms (BsmI, ApaI) in osteoporosis development.

Exclusion Criteria. The following exclusion criteria were applied: (1) studies describing cases in the pediatric population, (2) studies where full-text access was unavailable for review, (3) case reports, case series, and commentaries, (4) studies published in languages other than English, (5) studies that did not investigate VDR gene polymorphisms, (6) studies published before 2014.

Article Selection

The article selection for this review was conducted by the authors, who identified relevant studies and excluded those that did not meet the inclusion criteria. The next stage of our research involved reviewing and analyzing the selected articles.

For the PubMed database search, three types of queries were used:

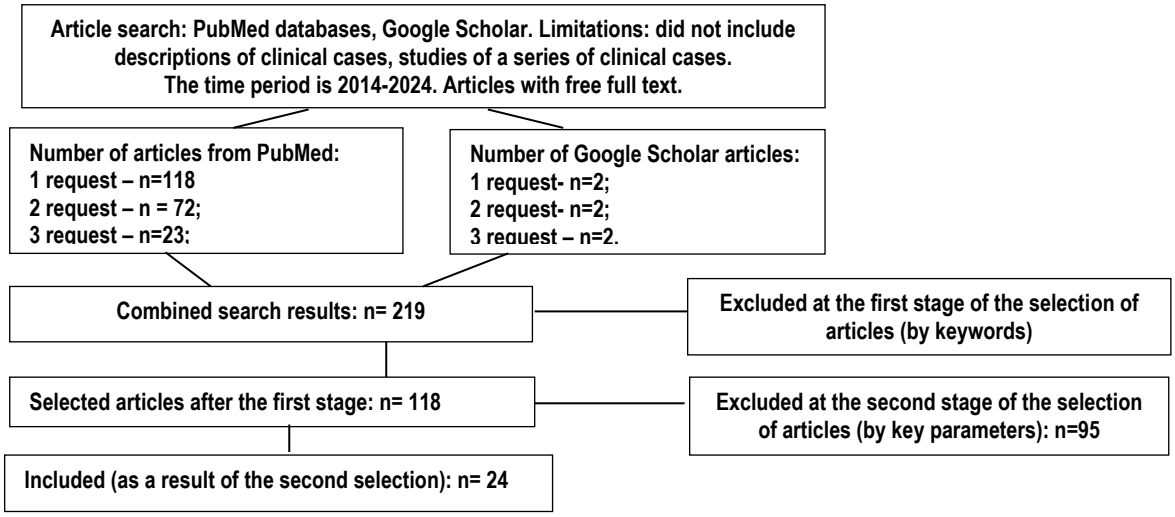
1. "Osteoporosis and VDR"
2. "Osteoporosis and VDR polymorphisms"
3. "Osteoporosis and vitamin D receptor polymorphisms in women"

For the Google Scholar database search, three types of queries were applied:

1. Allintitle: Osteoporosis and VDR
2. Allintitle: Osteoporosis and VDR polymorphisms
3. Allintitle: Osteoporosis and vitamin D receptor polymorphisms in women.

Ethical Statement

Our analysis is based on studies previously conducted by other authors; therefore, no ethical committee approval or patient informed consent was required for this review.



Discussion

Postmenopausal osteoporosis (PMO) is the most common form of primary osteoporosis, affecting women during menopause. The clinical significance of osteoporosis lies in its severe complications, such as low-energy fractures, which significantly increase the risk of morbidity and mortality, particularly in elderly individuals. The impact of osteoporosis on human health is substantial, with more than 9 million osteoporotic fractures recorded worldwide each year [11].

The pathogenesis of osteoporosis is complex, involving multiple factors, among which genetic factors play a particularly important role. It is estimated that up to 90% of osteoporosis predisposition may be genetically determined [24].

Table 1.

Association of the ApaI (rs7975232) Polymorphism of Vitamin D in Different Populations (2014–2024).

№	Author, year of publication	Country	Total sample	Genotype	AOR	p-value
1	Marozik P. et al. 2021	Belarus	602	A/A	1,9 (1,2–3,1)	< 0,05
2	Ansari M.G.A. et al. 2021	UAE	600	A/C	1,6 (1,1–2,3)	< 0,023
3	Yaghoobi M.M. et al. 2024	Iran	82	A/A	0.9 (0.471-1.742)	< 0.767
4	Meng D. et al. 2018	China	336	A/A	0.7(0.513-1.325)	< 0,946
5	Dehghan M. et al. 2016	Iran	200	A/A	1,8 (1,3–2,9)	> 0,05

Table 2.

Data on the association of BsmI (rs1544410) vitamin D polymorphism in Different Populations (2014-2024).

№	Author, year of publication	Country	Total Sample	Genotype	AOR	p-value
1	Marozik P. et al. 2021	Belarus	602	T/T	1,9 (1,2–3,1)	< 0,05
2	Ansari M.G.A. et al.2021	UAE	600	C/T	1,6 (1,1–2,3)	< 0,023
3	Yaghoobi M.M. et al.2024	Iran	82	A/A	0.9 (0.471-1.742)	< 0.767
4	Techapatiphandee et al. 2018	Thailand	237	A/A	0,31 (0,01–2,98)	< 0,26
5	Dehghan M. et al. 2016	Iran	200	A/A	1,7 (1,3–2,9)	> 0,05
6	Moran J.M. et al. 2015	Spain	210	A/A	1,9 (1,42–3,26)	> 0,05

The VDR ApaI polymorphism is located in the 3rd regulatory region of the VDR gene (in intron 8), leading to changes in the biological functions of vitamin D [22]. The VDR gene is located on chromosome 12q12-14 and consists of eight exons encoding the protein (exons 2–9) and six alternatively spliced untranslated exons (1a–1f). SNPs and point mutations frequently occur in introns or in the 3'untranslated region (UTR) of the VDR gene. Changes in these regions can affect transcriptional regulation, mRNA stability, or protein translation efficiency, ultimately influencing VDR protein levels [19].

The VDR receptor belongs to the nuclear receptor family of ligand-activated transcription factors and regulates downstream target genes involved in various biological functions, including calcium and phosphate homeostasis in bone metabolism. Given the importance of VDR in mediating the effects of vitamin D, its study is a crucial focus for understanding the pathogenesis of musculoskeletal diseases, particularly osteoporosis [10].

In their study, *Meng D. et al.* (2018) investigated the association between the VDR ApaI polymorphism and osteoporosis risk in postmenopausal Han Chinese women from the Xinjiang region. A total of 336 women participated in the study. No significant differences were found in the genotype frequencies of ApaI between the osteoporosis group (90 cases) and the non-osteoporosis group (246 cases) (P = 0.946). This study did not analyze the association between osteoporosis and the BsmI polymorphism. Based on their findings, the authors concluded that the VDR ApaI single nucleotide polymorphism (SNP) is associated with osteoporosis risk in women of European and African descent [13]. However, no significant association was identified between the VDR ApaI polymorphism and bone mineral density (BMD) at specific

skeletal sites in postmenopausal Han Chinese women (Table 1).

Morozik P. et al. (2021) examined the association between specific VDR gene variants and osteoporosis risk in postmenopausal Belarusian women. The study included 602 women, divided into an osteoporosis group (355 women) and a control group (247 women), followed by clinical examination and genetic testing. The study found that the BsmI (rs1544410) T/T genotype was significantly more prevalent among osteoporosis patients (27.9%) compared to the control group (17.0%) (OR = 2.4, 95% CI 1.5–3.8, P = 0.0028) (Table 2). Additionally, individuals in the osteoporosis group were more likely to carry the ApaI (rs7975232) A/A genotype (30.4%) compared to the control group (20.6%) (OR = 1.9, 95% CI 1.2–3.1, P = 0.0175) (Table 1) [11].

In 2021, Ansari MGA et al. conducted a study to investigate the role of the vitamin D receptor (VDR) gene in osteoporosis development. The study included 600 postmenopausal Saudi women (300 with osteoporosis and 300 controls), recruited from various primary healthcare centers (PHCCs) in Riyadh, Saudi Arabia. The study results showed that the heterozygous A/C genotype of ApaI (rs7975232) (OR = 1.6, 95% CI 1.1–2.3, P < 0.023) and the C/T genotype of BsmI (rs1544410) (OR = 1.6, 95% CI 1.1–2.4, P < 0.022) were significantly associated with an increased risk of osteoporosis, independent of age and BMI [2].

Yaghoobi M.M. et al. (2024) examined the potential association between six single nucleotide polymorphisms (SNPs) in the VDR gene (rs11568820, rs4516035, rs2228570, rs1544410, rs7975232, and rs731236) and the development of osteoporosis in Kerman Province, Iran [21].

The study included 82 individuals from southeastern Iran, divided into two groups: osteoporosis patients (n = 40) and control subjects (n = 42). The authors highlighted the significance of VDR genetic polymorphisms in osteoporosis risk in this specific population.

Another study from Iran, conducted by *Dehghan M. et al.* (2016), examined 200 individuals from southwestern Iran (130 patients and 70 healthy controls). Statistical analysis did not reveal a significant association between the ApaI polymorphism and bone mineral density (BMD) in the femoral neck and lumbar spine (P < 0.05). However, the distribution of BsmI genotypes among osteoporosis patients was as follows: Bb genotype: 70 (53.8%), BB genotype: 31 (23.8%), bb genotype: 29 (22.3%). In the control group, the distribution was: Aa genotype: 39 (55.7%), AA genotype: 14 (20%), aa genotype: 17 (24.3%). Statistical analysis showed a significant association between the BsmI polymorphism and BMD in the femoral neck (P < 0.05), but no significant association with BMD in the lumbar spine (P > 0.05) [23].

In the study by *Israr Ahmad et al.* (2018), the genotypic and allelic frequency distribution of VDR ApaI between osteoporosis patients and controls did not show any significant differences [9].

In 2015, *Moran J.M. et al.* conducted a study involving 150 postmenopausal Spanish women with osteoporosis, 30 women with osteopenia, and 30 healthy controls. The objective was to assess the association between the VDR BsmI polymorphism and bone mineral density (BMD) [14].

The study concluded that the BsmI polymorphism in the VDR gene was not associated with BMD in Spanish women [17].

Postmenopausal osteoporosis (PMO) is a common condition requiring intensive treatment, with effects measurable only over a long period, and its primary goal is to prevent bone fractures [20]. The key mechanisms of genetic variability in the vitamin D receptor (VDR) associated with bone mineral density (BMD) and osteoporosis remain unclear [8]. Genetic factors primarily influence bone size, mass, structure, microstructure, and intrinsic characteristics, with 60–80% of peak bone mass determined by genetic factors [7]. Numerous studies, including meta-analyses, have investigated the relationship between VDR gene polymorphisms and osteoporosis diagnosed using dual-energy X-ray absorptiometry (DXA). BMD assessment via DXA is the gold standard for diagnosing osteoporosis, as recommended by the World Health Organization (WHO) [3].

Several other VDR gene polymorphisms have also been identified. The VDR gene contains allelic variants recognized by restriction endonucleases: ApaI (allele A/a CA), TaqI (allele T/t TC), BsmI (allele B/b GA), and FokI (allele F/f CT), which have been reported to be associated with BMD [17]. In a study by Techapatiphandee M. et al., the association of three SNPs in VDR (TaqI, BsmI, and FokI) with osteoporosis was evaluated. The study found that the VDR TT genotype in the FokI SNP was a risk factor for osteoporosis, whereas no significant association was found between the TaqI and BsmI SNPs and osteoporosis among Thai patients. Similarly, studies have reported inconsistent results regarding the associations of VDR FokI and BsmI polymorphisms with osteoporosis risk. These discrepancies may be attributed to small sample sizes, racial differences, regional variations, and sampling methods. Other meta-analyses [6] have reported an association between VDR BsmI, FokI, and Cdx2 polymorphisms and osteoporosis risk [18].

A meta-analysis conducted by *Mu Y. et al.* (2022) found no significant association between the VDR BsmI polymorphism and the risk of osteoporotic fractures (p > 0.05) across all genetic models [15]. The study did not establish a link between the VDR BsmI polymorphism and osteoporosis and could not determine whether the VDR ApaI polymorphism significantly increases the risk of osteoporotic fractures (p > 0.05 in all genetic models) among Europeans.

To date, no studies have analyzed the association between VDR gene polymorphisms and osteoporosis in the Kazakh population.

Conclusion

Although some studies on various populations have identified an association between several VDR gene polymorphisms and bone mineral density (BMD), many questions in this area remain unresolved. Research on VDR gene polymorphisms has shown that their impact on low BMD can yield different results across populations.

Identifying VDR gene polymorphisms could help identify individuals at high risk for osteoporosis (OP) in the Kazakh population. Such genetic studies could assist in diagnosing the risk of OP development in pre- and postmenopausal women, formulating a comprehensive prevention strategy

for at-risk groups, and assessing the effectiveness of therapy.

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