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Vitamin D receptor gene polymorphism in women with genital endometriosis, type 1 diabetes mellitus, and in the population

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AIM: The aim of this study was to analyze the association between the vitamin D receptor gene polymorphism and the risk of developing genital endometriosis and type 1 diabetes mellitus.

MATERIALS AND METHODS: The frequency of allelic variants of the *VDR* gene was studied by PCR-RFLP analysis in 282 women, including 129 patients with genital endometriosis (stages I–IV), 71 patients with type 1 diabetes mellitus, and 82 women of the control group represented by the population sample.

RESULTS: It was found that the frequency of the allele *G* polymorphic variant of rs1544410 (BsmI) in the *VDR* gene was significantly higher in the group of patients with genital endometriosis compared to the population sample ($p = 0.048$). Significant differences for the G / G genotype in patients with genital endometriosis relative to the control group ($p < 0.05$) and the group of patients with type 1 diabetes mellitus ($p < 0.05$) were revealed. According to the odds ratio, the risk of developing genital endometriosis was 1.9 times higher for this genotype (OR = 1.93 CI = 1.082–3.450; OR = 1.892 CI = 1.022–3.430). The combination of the A / A and G / A genotypes was significantly more common in patients with type 1 diabetes mellitus ($p = 0.040$) and in the population ($p = 0.025$), when compared to the patients with genital endometriosis. A significant increase in the t allele of the rs731236 polymorphism (TaqI) of the *VDR* gene was found in the group of patients with type 1 diabetes mellitus ($p < 0.05$). The combination of the T / t and t / t genotypes of the rs731236 polymorphism (TaqI) of the *VDR* gene in patients with type 1 diabetes mellitus were significantly more common than in the group of patients with genital endometriosis ($p = 0.017$).

CONCLUSIONS: The data obtained may be important for risk assessment of genital endometriosis and type 1 diabetes mellitus development and for developing new strategies for the prevention and treatment of these diseases.

Keywords: vitamin D; vitamin D receptor (VDR); *VDR* gene; *VDR* gene polymorphism; genital endometriosis; type 1 diabetes mellitus.

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Анализ полиморфизма гена рецептора витамина D (*VDR*) у женщин с наружным генитальным эндометриозом, сахарным диабетом 1-го типа и в популяции

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Цель — проанализировать ассоциации полиморфизма гена рецептора витамина D (*VDR*) с риском развития наружного генитального эндометриоза и сахарного диабета 1-го типа.

Материалы и методы. Методами полимеразной цепной реакции и полиморфизма длин рестрикционных фрагментов исследованы частоты аллельных вариантов гена *VDR* у 282 женщин, из них — 129 больных наружным генитальным эндометриозом I–IV степеней, 71 пациентка с сахарным диабетом 1-го типа и 82 женщины контрольной группы, представленной популяционной выборкой.

Результаты. Частота аллеля *G* полиморфного варианта rs1544410 (BsmI) гена *VDR* была достоверно выше в группе пациенток с наружным генитальным эндометриозом по сравнению с популяционной выборкой ($p = 0,048$). Выявлены достоверные различия для генотипа G/G у больных наружным генитальным эндометриозом относительно группы контроля ($p < 0,05$) и группы больных сахарным диабетом 1-го типа ($p < 0,05$). Согласно коэффициенту отношения шансов риск развития наружного генитального эндометриоза в 1,9 раза выше при данном генотипе (ОШ 1,93; ДИ 1,082–3,450; ОШ 1,892; ДИ 1,022–3,430). Сочетание генотипов A/A+G/A достоверно чаще встречается у больных сахарным диабетом 1-го типа ($p = 0,040$) и в популяции ($p = 0,025$) по сравнению с пациентками с наружным генитальным эндометриозом. Обнаружено достоверное увеличение встречаемости t-аллеля полиморфизма rs731236 (TaqI) гена *VDR* в группе пациенток с сахарным диабетом 1-го типа ($p < 0,05$). Сочетания генотипов T/t+t/t полиморфизма rs731236 (TaqI) гена *VDR* у больных сахарным диабетом 1-го типа отмечены достоверно чаще, чем в группе пациенток с наружным генитальным эндометриозом ($p = 0,017$).

Заключение. Полученные данные могут быть важны для оценки риска развития наружного генитального эндометриоза и сахарного диабета 1-го типа и разработки новых стратегий профилактики и лечения данных заболеваний.

Ключевые слова: витамин D; рецептор витамина D (VDR); ген *VDR*; полиморфизм гена *VDR*; наружный генитальный эндометриоз; сахарный диабет 1-го типа.

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BACKGROUND

The term "vitamin D" represents a group of chemically similar substances. Contemporary research showed that vitamin D is not only essential for the normal development and functioning of the bone tissue but is also a hormone that causes various changes in many tissues and organs. The active hormonal form of vitamin D, calcitriol ($1,25[OH]_2D$, 1,25-dihydroxy vitamin D, 1,25-dihydroxy vitamin D_3) is formed as a result of two successive hydroxylation reactions and binds to specific vitamin D receptors (VDR), with various biological effects, such as hypotensive, lipolytic, normoglycemic, anabolic, antidepressant, analgesic, anti-inflammatory, immunomodulatory, and antiproliferative effects, and also regulates apoptosis and angiogenesis. These effects are classified as "non-classical." The VDR is encoded by the VDR gene, which has several polymorphic variants. The most significant and studied polymorphic variants of the VDR gene associated with several disease development are rs1544410 (BsmI), rs2228570 (FokI), rs731236 (TaqI), and rs7975232 (ApaI) [1] (Figure).

Genital endometriosis is registered in 10% of women of reproductive age worldwide. This disease most commonly manifests itself as pain and infertility. On average, the delay in diagnosing patients with external genital endometriosis (EGE) is approximately 8–10 years [2]. The problem of late EGE diagnosis is mainly associated with the variety of clinical manifestations and absence of non-invasive highly specific markers that determine the presence of the disease, as well as necessary intraoperative and morphological diagnosis confirmation. EGE is caused not by mutations of single genes, but rather unfavorable combinations of allelic variants of several different genes (gene network) that control endometrial morphogenesis processes, which is typical for multifactorial diseases [3]. Precisely due to its non-classical effects, the colecalciferol is believed to directly affect the EGE pathogenesis and can be used as its drug therapy. A number of works, both *in vitro* and based on experimental models in animals, demonstrate the positive effect of colecalciferol on endometrioid foci [4–7]. Data on the effect of colecalciferol on pain syndrome, psycho-emotional background stabilization, and fertility improvement are controversial [8–11].

Epidemiological data indicate the involvement of vitamin D deficiency in the pathogenesis of type 1 diabetes mellitus (DM). Polymorphisms in genes essential for vitamin D metabolism also modulate the risk of type 1 DM. J. Cooper et al. revealed a relationship between single nucleotide polymorphisms (SNPs) rs10741657 and rs12794714 in the *CYP2R1* gene and the risk of occurrence of type 1 DM [12]. The United Kingdom case-control study, involving 7854 patients with type 1 DM and 8758 healthy participants, revealed an association between the two SNPs (rs10877012 and rs4646536) in the *CYPB1* gene encoding vitamin D 1α-hydroxylase and type 1 DM [13]. The GG genotype of *CYP2R1* (SNP rs10741657) or the CC genotype of *CYP27B1* (SNP rs10877012) was found to increase the risk of type 1 DM [14]. In people with a combination of these two genotypes, the risk of type 1 DM was significantly higher than that with only one genotype, which indicates a potential synergy between the GG genotype of *CYP2R1* and the CC genotype of *CYP27B1* in determining the risk of type 1 DM. Serum vitamin D (25[OH]D) levels were significantly lower in patients with the GG genotype of *CYP2R1* and the CC genotype of *CYP27B1* compared to those with the *CYP2R1* AA and *CYP27B1* AA genotypes. An assumption was made about the potential role of *VDR* gene polymorphisms in the pathogenesis of type 1 DM.

A major TEDDY study was conducted in 6 United States and 5 European countries from 2004 to 2010 [15]. A total of 424,788 newborns were examined. The study included 8,676 children with an increased risk of type 1 DM (Abs GADA, IAA, and IA-2A), having first-line relatives with type 1 DM and those without relatives with type 1 DM. The study started in children aged 4 months. The follow-up period was 6 years. The polymorphism in genes *VDR*, *CYP24A*, *CYP27B1*, *GC*, and *RXR* was analyzed. Vitamin D deficiency based on the determination of the blood serum level of 25(OH)D was established in 42% of children and 22%–67% of children with type 1 DM. The highest plasma concentrations of 25(OH)D and a low risk of developing type 1 DM were revealed in children with the minor allele of the *VDR rs7975232* (ApaI).

G. Tapija et al. [16] believe that a higher level of 25(OH)D in cord blood can be considered a favorable prognostic factor to reduce the risk of developing type 1 DM in children homozygous for the *VDR* rs11568820 (Cdx2) G/G genotype. N. Habibian et al. demonstrated an association between an increased risk of type 1 DM and some polymorphic variants in the *VDR* gene (especially BsmI and FokI). A sufficient level of 25(OH)D in the blood serum (≥30 ng/ml) in combination with some SNP genotypes (TaqI and BsmI) in the *VDR* gene in patients with newly diagnosed type 1 DM was established

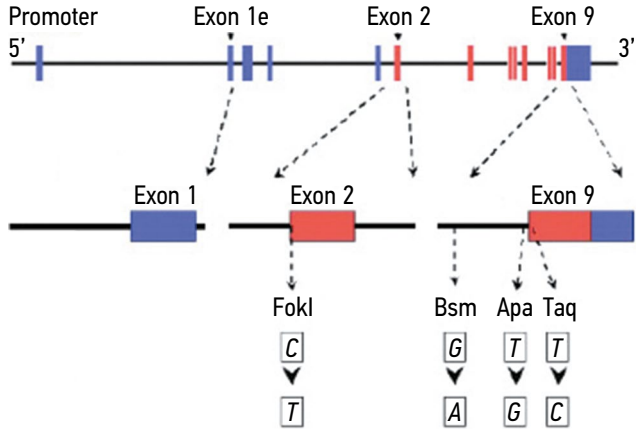

Figure. Polymorphic variants and structure of the *VDR* gene: FokI, BsmI, ApaI, TaqI — sites for recognition of the corresponding restriction endonucleases

to contribute to the functional preservation of residual beta cells in the pancreas [17]. Research results suggest that SNPs in genes important for synthesis, transportation, and action of vitamin D may influence the risk of developing type 1 DM.

The work aimed to analyze the association of the *VDR* gene polymorphism with the risk of EGE and type 1 DM.

MATERIALS AND METHODS

A total of 282 female patients were enrolled in the study, including 129 patients with grade I–IV genital endometriosis that are confirmed intraoperatively and morphologically, 71 patients with type 1 DM, and 82 female patients of the control group represented by the population sample. The exclusion criteria were severe concomitant somatic pathology and cancer.

DNA from peripheral blood lymphocytes was isolated by the standard salt method with some modifications. The frequencies of allelic variants of the *VDR* gene were studied using the polymerase chain reaction (PCR) with restriction fragment length polymorphism.

The following primers were used to amplify a fragment of the promoter region of the *VDR* gene:

- VDR rs2228570 F GTATGAGGGCTCCGAAGGCA
- VDR rs2228570 R GAAGGAGATGTGAAAAATGCAAG
- VDR rs1544410 F CCCTCACTGCCCTTAGCTCT
- VDR rs1544410 R TAACTTCCTCTTCGGCCTTT
- VDR rs731236 F 5'- GATGATCCAGAAGCTAGCCGACCT-3'
- VDR rs731236 R 5'- GCAACTCCTCATGGCTGAGGTCT-3'

PCR conditions are presented in Table 1.

Restriction of the amplified DNA fragments was performed according to the manufacturer's recommendations (Sibenzyme).

PCR products were hydrolyzed with a restriction endonuclease (Table 2) at 37°C for 16 h in 10 μl of reaction mixture containing 5 μl of amplification agent, 3 μl of water, 1 μl × 10 of buffer recommended by the manufacturer for each restriction endonuclease, and 10 units (0.5 μl) of restriction endonuclease.

The completeness of hydrolysis was assessed by the results of electrophoresis in 7.5% polyacrylamide gel. Images were captured using a video gel documentation system (Vilber Lourmat).

Statistical data processing was performed using the standard approaches used in population genetic studies. The significance of the frequency differences was determined using the exact two-tailed Fisher's test using the standard formula, taking into account the Yates correction for paired comparisons with the control group. The chi-square test (χ^2) with the use of the standard formula, taking into account the Yates correction for paired comparisons. The Bonferroni correction was used for multiple comparisons with the control group. The odds ratio (OR) was also applied for significant differences between the control and the study groups. The OR value concerning our

Table 1. Conditions for the polymerase chain reaction

Polymorphic variants of the *VDR* gene	Denaturation	Denaturation	Renaturation	Synthesis
		12 cycles	20 cycles	
rs2228570 (FokI)	94°C — 7 min	96°C — 15 s 65°C — 20 s	96°C — 15 s 62°C — 20 s 76°C — 15 s	72°C — 5 min
rs1544410 (BsmI)	94°C — 7 min	96°C — 15 s 65°C — 20 s	96°C — 15 s 62°C — 20 s 76°C — 15 s	72°C — 5 min
rs731236 (TaqI)	94°C — 7 min	96°C — 15 s 65°C — 20 s	96°C — 15 s 62°C — 20 s 76°C — 15 s	72°C — 5 min

Table 2. Restriction endonucleases and analysis of polymorphic variants of the *VDR* gene

Polymorphic variants of the *VDR* gene	Size of the PCR product	Endonuclease	Allele and size of restriction fragments
rs1544410 (BsmI)	320 bp	HspA I	A — 320 bp G — 216 + 104 bp
rs2228570 (FokI)	429 bp	BstF5I	T — 101 + 91 + 237 bp C — 101 + 328 bp
rs731236 (TaqI)	360 bp	Taq I	T — 360 bp t — 248 + 112 bp

Note: bp — base pairs; PCR — polymerase chain reaction.

data shows the extent probability of a given genotype in patients exceeding the probability of its presence in the control group or the extent of the probability of having a particular disease with a certain genotype is higher.

The OR value was calculated using the formula:

$$OR = a/b \times d/c,$$

where *a* is the number of individuals with this marker in the study group; *b* is the number of individuals without this marker in the study group; *c* is the number of individuals with this marker in the control group; and *d* is the number of individuals lacking this marker in the control group.

OR is indicated with a 95% confidence interval (CI). The CI boundaries were calculated by the formulas:

$$OR_{min} = OR^{(1 - 1,96/\sqrt{x^2})} \text{ and } OR_{max} = OR^{(1 + 1,96/\sqrt{x^2})}.$$

Differences were considered statistically significant at a *p*-value of <0.05.

RESULTS

In the present study, the frequencies of alleles and genotypes were determined for the polymorphic variants rs1544410 (BsmI), rs2228570 (FokI), and rs731236 (TaqI) of the *VDR* gene.

The analysis revealed that in the group of patients with EGE, the most common genotypes were G/G (47.3%) of the rs1544410 (BsmI) polymorphism, C/T (45.7%) of the rs2228570 (FokI) polymorphism, and T/T (49.6%) of the rs731236 (TaqI) polymorphism of the *VDR* gene. In the group of patients with type 1 DM, the most common genotypes were G/A (53.5%) of polymorphism rs1544410 (BsmI), C/T (40.9%) of polymorphism rs2228570 (FokI), and T/t (53.5%) of polymorphism rs731236 (TaqI); whereas in the control group, they were G/A (52.4%) of the rs1544410 (BsmI) polymorphism, C/T (47.6%) of the rs2228570 (FokI) polymorphism, and T/t (45.1%) of the rs731236 (TaqI) polymorphism of the *VDR* gene.

Table 3. Frequency distribution of genotypes and alleles of polymorphic variants of the *VDR* gene in patients with external genital endometriosis, type 1 diabetes mellitus, and the control group

Polymorphic variant of the *VDR* gene			External genital endometriosis		Type 1 diabetes mellitus		Control group		*p*
			n	%	*n*	%	*n*	%	
rs1544410 (BsmI)	Genotypes	*A/A*	16	12.4	10	14.1	13	15.9	
		G/A	52	40.3	38	53.5	43	52.4	
		G/G	61	47.3	23	**32.4***	26	**31.7****	<0.05* OR 1.892 CI 1.022–3.430 0.05** OR 1.932 CI 1.082–3.450
		A/A+G/A	68	52.7	48	**67.6***	56	**68.3****	0.04* 0.025** OR 0.52 CI 0.29–0.92
		Total	129	100	71	100	82	100	
	Alleles	*A*	84	**32.6**	58	40.8	69	**42.1**	
		G	174	**67.4**	84	59.2	95	**57.9**	0.048
rs2228570 (FokI)	Genotypes	*C/C*	37	28.7	28	39.4	22	26.8	
		C/T	59	45.7	29	40.9	39	47.6	
		T/T	33	25.6	14	19.7	21	25.6	>0.05
		Total	129	100	71	100	82	100	
	Alleles	*C*	133	51.6	85	59.9	83	50.6	
		T	125	48.4	57	40.1	81	49.4	>0.05
rs731236 (TaqI)	Genotypes	*T/T*	64	49.6	23	32.4	33	40.3	
		T/t	51	39.5	38	53.5	37	45.1	
		t/t	14	10.9	10	14.1	12	14.6	>0.05
		T/t+t/t	65	**50.4**	48	**67.6**	49	59.7	0.017
		Total	129	100	71	100	82	100	
	Alleles	*T*	179	69.4	84	59.2	103	62.8	
		t	79	30.6	58	**40.8**	61	37.2	<0.05

Note. Values are presented in bold if statistically significant differences were revealed upon comparison.

The statistical data processing revealed a significantly higher frequency of the G allele of the polymorphic variant rs1544410 (BsmI) of the *VDR* gene in the group of patients with EGE compared with the population sample ($p = 0.048$). Significant differences were found in the G/G genotype in patients with EGE relative to the control group ($p < 0.05$) and the group of patients with type 1 DM ($p < 0.05$). According to the OR coefficient, the risk of EGE is 1.9 times higher for this genotype (OR 1.93 CI 1.082–3.450; OR 1.892 CI 1.022–3.430). The combination of genotypes A/A + G/A is significantly more common in patients with type 1 DM ($p = 0.04$) and the population ($p = 0.025$) compared to patients with EGE.

Based on the data presented in Table 3, the analyses of the rs2228570 (FokI) polymorphic variant of the *VDR* gene found no significant differences.

The study revealed a significantly increased frequency of occurrence of the t-allele of the rs731236 (TaqI) polymorphism of the *VDR* gene in the group of female patients with type 1 DM ($p < 0.05$). Combinations of genotypes T/t + t/t of the rs731236 (TaqI) polymorphism of the *VDR* gene in patients with type 1 DM were significantly noted more often than in the group of patients with EGE ($p = 0.017$).

DISCUSSION

Only a few studies are currently focused on the analysis of *VDR* gene polymorphism in patients with EGE. A group of Brazilian scientists suggested that genetic alterations in the *VDR* gene could lead to significant defects in gene activation and thus affect immune function. The authors investigated the possible relationship between endometriosis and/or infertility and *VDR* gene polymorphisms (ApaI, TaqI, FokI, and BmsI). Study results indicate that the *VDR* gene polymorphism does not play an important role in the pathogenesis of endometriosis and/or infertility in the studied Brazilian women [18]. Another work of this group of authors assessed the frequencies of the FokI polymorphism of the *VDR* gene in infertile women with endometriosis and its relationship with the disease. Study results showed that the FokI polymorphism of the *VDR* gene is not associated with infertility caused by endometriosis in Brazilian women [19].

A group of Polish scientists, investigating the genetic risk factors for infertility associated with endometriosis, revealed that the frequencies of genotypes and alleles did not differ significantly in the main and control groups, but the A-T (BmsI-FokI) haplotype (OR 1.659 [1.122–2.453], $p = 0.011$) of the *VDR* gene was identified as a risk factor for infertility associated with endometriosis [20].

Our study established that the G/G genotype of the rs1544410 (BsmI) polymorphic variant of the *VDR* gene increases the risk of EGE by 1.9 times. According to the literature data, the A allele of this polymorphism is associated with increased expression of the *VDR* gene and increases the serum level of the active hormonal form of vitamin D, calcitriol, compared with variant G [21]. In addition, variant G predominates among patients with EGE, which is probably associated with decreased gene expression and serum calcitriol levels. This fact may be important when choosing the dose of the drug for this category of patients.

Our study found a significantly increased frequency of occurrence of the t-allele of the rs731236 (TaqI) polymorphism of the *VDR* gene in the group of patients with type 1 DM ($p < 0.05$), which is consistent with the literature data, although studies on this issue are limited. A.E. Ahmed et al. [22] studied the relationship between SNPs Fok I F > f (rs10753810), Bsm I B > b (rs1544410), Apa I A > an (rs7975232), and Taq I T > t (rs731236) in the *VDR* gene and type 1 DM in children. The BsmI B and ApaI A polymorphisms were associated with the risk of type 1 DM. Deficient vitamin D was registered more often in patients with DM. When vitamin D was added to standard insulin therapy, a significant improvement in the glycemic profile was noted. O.A. Sahin et al. [23] analyzed 9 studies that included 1,053 pediatric patients with type 1 DM and the control group consisted of 1,017 children without DM. The results showed that the BsmI BB, BsmI Bb, and TaqI tt polymorphisms were associated with an increased risk of type 1 DM, whereas such polymorphic variants as BsmI Bb and TaqI tt, contrarily, were associated with a protective effect on the disease development.

The meta-analysis and systematic review, which combined 40 studies, aimed to assess the associations between polymorphisms FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) of the *VDR* gene and the predisposition to the development of type 1 DM. The authors failed to identify a significant relationship between the *VDR* gene SNP and the risk of type 1 DM in the population [24]. However, when analyzing these associations in various subgroups, a significant association was found between the FokI and BsmI polymorphisms and the risk of type 1 DM in the African and American populations.

Polymorphisms of genes that are involved in the synthesis of vitamin D and encode its hydroxylases, *VDBR* and *VDR*, can increase the risk of developing type 1 DM. Therefore, an extension study is required to assess their influence on vitamin D status and its effects. This will identify the groups of patients who need higher doses of vitamin D to achieve the desired target serum 25(OH)D values to prevent and treat type 1 DM. Further studies of *VDR*, in addition to genetic and traditional risk factors for the development of type 1 DM, will make it possible to identify new critical factors that can be further applied in personalized medicine for diagnosis and more optimized and higher quality treatment of such patients.

Thus, the obtained data are important for assessing the risk of developing EGE and type 1 DM and developing new strategies for the prevention and treatment of these diseases; however, further research is required in this field.

ADDITIONAL INFORMATION

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Author contributions. *T.E. Ivaschenko* and *M.I. Yarmolinskaya* created the concept and design, wrote and edited the text. *A.S. Denisova, A.A. Shagina,* and *E.V. Misharina* collected and processed material. *T.E. Ivaschenko* and *A.S. Denisov* processed the statistical data. *A.S. Denisova* and *E.V. Misharina* wrote the text.

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