The VDR gene FokI polymorphism is associated with gestational diabetes mellitus in Turkish women

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Abstract

Background: The association between the vitamin D receptor (VDR) gene and gestational diabetes mellitus (GDM) has not been investigated in Turkish pregnant women. We aimed to investigate associations between VDR gene BsmI (rs15444410), ApaI (rs7975232), FokI (rs19735810), and TaqI (rs731236) single nucleotide polymorphisms (SNPs) and GDM.

Material-methods: This case-control study comprised 100 women with GDM and 135 pregnant women without GDM. The VDR polymorphism was evaluated using Sanger-based DNA sequencing.

Result: VDR gene ApaI, BsmI, and TaqI SNPs did not differ between women with and without GDM (each, \(p > 0.05\)). ApaI, BsmI, and TaqI were not associated with GDM risk. The VDR gene FokI CT/TT genotype was associated with an increased GDM risk (CT vs. CC, \(OR = 1.84, 95\% CI: [1.05–3.23], p = 0.031\); TT vs. CC, \(OR = 3.95, 95\% CI: [1.56–9.96], p = 0.002\); CT/TT vs. CC, \(OR = 2.29, 95\% CI: [1.35–3.89], p = 0.002\); and CT/CC vs. TT, \(OR = 3.02, 95\% CI: [1.23–7.38], p = 0.012\). The FokI-TT genotype was more associated with younger age and higher glucose, HbA1c, and HOMA-IR than the CC and CT genotype. FokI-T was positively correlated with log-HOMA-IR (\(r = 0.326, p = 0.004\)). FokI SNPs were independently associated with GDM after adjusting for BMI and age (\(\beta = 1.63, 95\% CI: [1.24–2.42], p = 0.012\)). There were no associations between the FokI, ApaI, BsmI and TaqI haplotypes and GDM.

Conclusion: VDR gene FokI SNPs were independently associated with having GDM in Turkish women. VDR gene FokI SNPs might contribute to insulin resistance of developing GDM.

Keywords: VDR gene, FokI, Gestational diabetes

Background

Gestational diabetes mellitus (GDM) is defined as glucose intolerance diagnosed during pregnancy [1]. The prevalence of GDM shows differences among ethnic populations and ranges from 1 to 14% [2]. GDM is characterized by increased insulin resistance, hyperglycemia, and obesity [1, 3–5]. Genetic and environmental factors play an important role in the etiology of GDM [3]. Women with a family history of diabetes mellitus (DM) are at risk of GDM. Women with a history of GDM are at risk of type 2 DM (T2DM) in the future [1–5]. Genetic variations related to β-cell dysfunction and insulin resistance have been shown to contribute to the development of GDM [1, 3, 5, 6]. The vitamin D receptor (VDR) gene is actively involved in the insulin metabolic pathway. Vitamin D shows its cellular activity by binding to VDR. Vitamin D plays a role in insulin secretion [7]. Vitamin D deficiency was associated with pre-eclampsia, insulin resistance, and GDM [8]. Active vitamin D shows efficacy by binding to VDR and it has a wide range of genetic variations [9]. The complex of vitamin D and its receptor is a transcription factor that plays a role in the regulation of insulin secretion from pancreatic beta cells [10]. VDR acts as a ligand-dependent transcription factor and it is a member of the nuclear hormone receptor family. The VDR gene is localized on
chromosome 12q13.1, which consists of 11 exons [11–13]. This complex affects immune system regulation [11]. It has an effect on the proliferation, differentiation, and activation of immune cells and cytokine production, and accordingly, DM development [10–12]. Vitamin D deficiency leads to defects in insulin synthesis and secretion [10, 11, 13].

VDR polymorphisms have been associated with type 1 DM (T1DM) [11] and T2DM [13–15]. BsmI (A > G, rs1544410), Apal (A > C, rs7975232), TaqI (T > C, rs731236), and FokI (C > T, rs2228570) are human VDR single-nucleotide polymorphisms (SNPs). VDR gene BsmI, Apal, and TaqI SNPs are found in 3 prime untranslated regions where gene expression is regulated. FokI leads to T > C substitution at exon 2, thus the first translation initiation region is removed, and consequently transcriptional activity of VDR is changed [13, 16]. Both insulin resistance and impaired insulin secretion play a role in the pathogenesis of GDM and T2DM [10–12]. Vitamin D concentrations were measured. Insulin resistance was calculated using the homeostasis model assessment-insulin resistance (HOMA-IR): [fasting plasma insulin (μIU/mL) X fasting plasma glucose (mg/dL)] / 405 [20]. The study was approved by the Diskapi Yıldırım Beyazıt Teaching and Research Hospital Ethics Board (Number: 26.02.2015–12/21) and written consent was obtained from all participants.

Genotyping
Genetic analyses for VDR gene SNPs FokI (rs2228570), BsmI (rs1544410), Apal (rs7975232), and TaqI (rs731236) were performed using Sanger-based DNA sequencing. Genomic DNA was isolated from collected peripheral blood samples of the subjects using a DNA Isolation Kit (Roche Diagnostics, Indianapolis, IN, USA). Genotyping of each HNF1A gene polymorphism was independently performed using a prevalidated fluorescence-based allele-specific polymerase chain reaction (PCR) assay, KASPar (KBiosciences, Hoddesdon, UK), which was performed on a Rotor-Gene Q real-time cycler (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. Allele discrimination was made using Rotor-Gene Q software v2.3.1 (Qiagen, Hilden, Germany). The genotype identification was performed blind without information on clinical phenotypes.

Methods
Study population
Pregnant women who were referred to the Obstetrics and Gynecology Clinic of our tertiary hospital in Ankara from 2014 to 2015 were included in this case-control study. Women with GDM (n = 100) and non-diabetic pregnant controls (n = 135) were included. The pregnant women were aged 22–38 years and the pregnancy age was 24–28 weeks. Gestational age was assessed from the date of the last menstrual period and clinical assessment. A 2-hour, 75 g oral glucose tolerance test (OGTT) at 24 to 28 weeks’ gestation was performed for all pregnant women, irrespective of family history of DM or any other risk factors for GDM. Glucose concentrations after fasting, and 1 and 2 h after glucose administration < 92 mg/dL, < 180 mg/dL, and < 153 mg/dL, respectively, were considered normal. If a patient’s glucose concentration was higher than these values, the patient was diagnosed as having GDM [2].

Statistical analysis
Statistical analysis was performed using SPSS 18.0 (SPSS, Inc) software. Variables are presented as mean ± standard deviation (SD) or median (min-max), percentages (%), odds ratios (OR), 95% confidence intervals (CI). Normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk W test. SNPs are expressed as allelic frequency (q) or prevalence of genotypes (%). Categorical variables were analyzed using the Chi-square test or Fisher’s exact test, where appropriate. Student’s t-test was used for comparisons of normally distributed continuous variables or log-transformed variables between the two groups. The Hardy-Weinberg equilibrium (HWE) at individual loci was assessed using the Chi-square test. Multiple logistic regression analysis and Fisher’s exact test were tested using the following models: dominant (major allele homozygotes vs. heterozygotes + minor allele homozygotes), recessive (major allele homozygotes + heterozygotes vs. minor allele homozygotes) and codominant (major allele homozygotes vs. heterozygote and minor allele homozygotes vs. major allele homozygotes). Pair-wise linkage disequilibrium (LD) and correlation coefficients (r²) were analyzed using the HAPLOVIEW program. We made a variable reflecting all possible combinations of BsmI-Apal-TaqI genotypes for each SNP. Statistical significance was defined as a p < 0.05.
Results

Obesity (46.2 vs. 18.0%, *p* = 0.001) and insulin resistance (72.4 vs. 7.2%, *p* = 0.001) were higher in women with GDM than in the non-GDM controls. Serum glucose, insulin, HOMA-IR, HbA1c, BMI, and BPs were higher in the GDM group than in the control group (*p* < 0.05). 25(OH)D was lower in women with GDM than in the controls (*p* < 0.05). The characteristics of the pregnant women are shown in Table 1. The four SNPs in the control group were within the HWE. Minor allele frequency and the HWE are shown in Table 2.

The distributions of the VDR gene SNPs are shown in Table 3. The frequency of VDR gene *ApaI* rs7975232, *TaqI* rs731236 and *BsmI* rs1544410 did not differ between women with and without GDM in a codominant model and dominant model and recessive model (*p* > 0.05, each). VDR gene *ApaI*, *TaqI*, and *BsmI* SNPs were not associated with GDM. The frequency of VDR gene *FokI* rs2228570 differed between women with and without GDM (*p* < 0.05). Compared with the controls, *FokI* CT genotype (CT vs. CC, OR = 1.84, 95% CI: [1.05–3.23], *p* = 0.031) and TT (TT vs. CC, OR = 3.95, 95% CI: [1.56–9.96], *p* = 0.002) genotype were associated with an increased GDM risk in a codominant model, and CT/TT carriers had increased 2.2 odds of having GDM (CT/TT vs. CC, OR = 2.29, 95% CI: [1.35–3.89], *p* = 0.002) in a dominant model. Compared with the controls, TT genotype carriers had increased 3.02 odds of having GDM (CT/CC vs. TT, OR = 3.02, 95% CI: [1.23–7.38], *p* = 0.012) in a recessive model. Gestational age was lower in *FokI- TT* genotype compared with CC genotype (p < 0.05) (Table 4). *FokI-T* (risk allele) was positively correlated with log-HOMA-IR (r = 0.326, *p* = 0.004). In the logistic regression analysis, *FokI* SNPs were independently associated with GDM after adjusting for BMI and age (β = 1.63, 95% CI: [1.2–4.2], *p* = 0.012).

Discussion

This case-control study showed that VDR gene *FokI* SNPs were independently associated with having GDM in Turkish women. The frequency of the VDR gene *FokI* TT and CT genotype was increased in women with GDM compared with the non-GDM controls. The frequency of VDR gene *Apal*, *BsmI*, and *TaqI* SNPs did not differ between women with and without GDM with no association. VDR *FokI* SNPs might contribute to insulin resistance in the development of GDM.

Our results showed that 25(OH)D concentrations were lower in the GDM group than in the control group. Vitamin D deficiency was associated with insulin resistance and GDM [8]. The VDR gene has a role in the metabolic pathway of insulin [9]. VDR gene variations have been shown to be correlated in the development, progression, and complications of T2DM [13–15]. The present study showed that VDR gene *FokI* SNPs were independently associated with an increased risk of GDM in Turkish women (β = 1.63, 95% CI: [1.2–4.2], *p* = 0.012). Our study suggested that VDR gene *FokI* SNPs might be associated with having GDM. We found that the frequency of VDR gene *ApaI*, *TaqI*, and *BsmI* did not differ between women with and without GDM. VDR gene *ApaI*, *TaqI*, and *BsmI* SNPs were not associated with GDM. The VDR gene *FokI* SNPs showed significant differences between women with and without GDM. VDR gene *FokI* (variant or heterozygotes) compared to wild-type (CC) SNP revealed a significant association. VDR gene *FokI* rs2228570 TT (TT vs. CC, OR = 3.95, 95% CI: [1.56–9.96], *p* = 0.002) and CT heterozygotes (CT vs. CC, OR = 1.84, 95% CI: [1.05–3.239, *p* = 0.031) were associated with having GDM, compared with the controls. VDR gene *FokI* SNPs might contribute to developing GDM in the Turkish population.

Similar to our results, *FokI* homozygous SNPs were reported as prevalent in patients with DM and GDM [12, 13]. Aslani et al. reported that VDR gene *FokI* SNPs were associated with GDM in an Iranian population [12]. Another study reported that *ApaI* and *Taq* SNPs were associated with GDM in an Iranian population [16]. These results are incompatible with our study, thus we showed that *ApaI*, *Taq*, and *BsmI* SNPs were not associated with GDM. *BsmI* and *FokI* SNPs were not associated with T2DM in a Turkish population [15].
Dilmec et al. reported that *TaqI* SNPs were associated with T2DM, but *ApaI* and *FokI* SNPs were not associated with T2DM in a Turkish population [14]. Previous studies investigating the *VDR* gene in Turkish patients with T2DM were compatible with our study. Hence, we supposed that *Taq* and *ApaI* were not associated with having T2DM in the Turkish population.

VDR gene *Taq*, *BsmI* or *ApaI* SNPs were not associated with diabetic microvascular complications but only *FokI* SNPs were associated with diabetic neuropathy in a Caucasian population [13]. Meta-analysis reported that only *FokI* SNPs were found as a risk factor for T2DM. *Taq*, *BsmI* or *ApaI* SNPs were not associated with DM [21]. These reports were similar to the present study; we

### Table 2 Minor allele frequency and Hardy-Weinberg Equilibrium of VDR gene SNPs

| SNP       | Risk allele | MAF for study sample | p for HWE in control |
|-----------|-------------|-----------------------|----------------------|
| Apa I rs7975232 | C           | 0.54                  | 0.23                 |
| TaqI rs731236    | C           | 0.35                  | 0.78                 |
| BsmI rs15444410  | G           | 0.38                  | 0.15                 |
| FokI rs2228570   | T           | 0.29                  | 0.20                 |

*MAF* minor allele frequency, *HWE* Hardy-Weinberg Equilibrium

The Hardy-Weinberg equilibrium (HWE) at individual loci was assessed by Chi-Square test.

### Table 3 Genotype analysis of VDR gene SNPs

| SNP       | Non-GDM (n = 134) | GDM (n = 100) | OR (95% CI) | P     |
|-----------|-------------------|---------------|-------------|-------|
| ApaI rs7975232 (%)  |                  |               |             |       |
| Co-dominant Wild type AA | 19.4            | 17.0          | 1.04 (0.51–2.12) | 0.985 |
| Heterozygous AC      | 56.7             | 52.0          | 1.48 (0.67–3.25) | 0.326 |
| Homozygous CC        | 23.9             | 31.0          | 1.17 (0.59–2.30) | 0.639 |
| Dominant (AA/AC + CC)|                  |               |             |       |
| Recessive (AA+AC/CC) |                  |               |             |       |
| TaqI rs731236 (%)    |                  |               |             |       |
| Co-dominant Wild type TT | 40.0           | 44.0          | 0.76 (0.44–1.33) | 0.353 |
| Heterozygous CT      | 49.6             | 42.0          | 1.22 (0.52–2.84) | 0.633 |
| Homozygous CC        | 10.4             | 14.0          | 1.43 (0.80–2.56) | 0.225 |
| Dominant (TT/CT + CC)|                  |               |             |       |
| Recessive (TT + CT/CC)|                |               |             |       |
| BsmI rs15444410 (%)  |                  |               |             |       |
| Co-dominant Wild type AA | 31.9           | 42.0          | 0.58 (0.33–1.02) | 0.062 |
| Heterozygous AG      | 57.0             | 44.0          | 0.95 (0.41–2.22) | 0.916 |
| Homozygous GG        | 11.1             | 14.0          | 0.64 (0.37–1.10) | 0.109 |
| Dominant (AA/AG + GG)|                  |               |             |       |
| Recessive (AA+AG/GG) |                  |               |             |       |
| FokI rs2228570 (%)   |                  |               |             |       |
| Co-dominant Wild type CC | 60.0           | 41.0          | 1.84 (1.05–3.23) | 0.031 |
| Heterozygous CT      | 34.1             | 43.0          | 3.95 (1.56–9.96) | 0.002 |
| Homozygous TT        | 5.9              | 16.0          | 2.29 (1.35–3.89) | 0.002 |
| Dominant (CC/CT + TT)|                  |               |             |       |
| Recessive (CC + CT/TT)|                |               |             |       |

**GDM** gestational diabetes mellitus

SNPs were expressed as allelic frequency (q) or prevalence of genotypes (%)

Categorical variables were analyzed with Chi-square test or Fisher’s exact test, where appropriate.

Multiple logistic regression analysis and Fisher’s exact test were tested using models: dominant (major allele homozygotes vs heterozygotes + minor allele homozygotes), recessive (major allele homozygotes + heterozygotes vs minor allele homozygotes) and codominant (major allele homozygotes vs heterozygote and minor allele homozygotes vs major allele homozygotes)

Bold represents significant *p*-values
showed that only FokI SNPs were associated with having GDM. A meta-analysis showed that only BsmI SNPs were associated with autoimmune T1DM in an Asian population [11]. We supposed that autoimmunity might contribute to the association between BsmI SNPs and having T1DM. The inconsistency between studies might result from ethnic diversity and environmental factors on VDR variations in different populations [12].

The present study showed that the FokI-T (risk allele) was positively correlated with log-HOMA-IR. Assessment of allele frequency distribution showed a significant association of the FokI variant allele (T) on susceptibility toward GDM. We supposed that the FokI variant might contribute to impaired insulin resistance and metabolic disorder in developing GDM. Hence, FokI SNPs might have a role in the pathogenesis of GDM.

BsmI, Apal, and TaqI polymorphisms of the VDR gene are found in the three-primer untranslated region (3′-UTR) and have been shown to be in strong linkage disequilibrium (LD) [21]. The FokI polymorphism was reported as an independent marker of the VDR gene because it has not been shown to be in linkage disequilibrium with any other VDR polymorphisms [12]. Our study reported that VDR gene FokI, Apal, BsmI and TaqI haplotypes were not associated with GDM, and Apal, BsmI and TaqI polymorphisms were not shown in LD. Apal and BsmI polymorphisms of the VDR gene, both in intron 8, are considered as silent SNPs. These polymorphisms do not change the amino acid sequence of the encoded protein, but they might affect gene expression by modulating stability of mRNA [21]. The TaqI polymorphism is located at codon 352 in exon 9 of the VDR gene. The TaqI TT genotype (absence of restriction site) is related to lower active vitamin D3 [21]. The only locus with impact on the structure of VDR protein is the FokI polymorphism, which is located on the 5′ end region of the VDR gene. The VDR gene FokI polymorphism is functional because it is found in a coding sequence. The FokI polymorphism is located in the first ATG starting code of VDR protein. FokI is involved in thymine to cytosine (T/C) substitution at exon 2, the first translation initiation region is removed, and transcriptional activity of VDR is changed [12, 13, 16, 22]. It alters the ACG codon, which is found ten base pairs upstream from the translation starting codon and leads to the generation of an additional starting codon. Two different VDR isoforms occur with transition of allele T to C in ATG. When initiating translation starts from this alternative site in the thymine variant, it generates a longer VDR protein comprised of 427 amino acids. The gene is transcribed in normal length if there is a restriction site. Thus, the C/C allele codes a 424-amino acid protein and the T/T allele codes a 427-amino acid protein. The longer VDR protein has low activity in transcription, accordingly activation is decreased in target cells [12, 13]. The FokI T/T genotype, FokI C/C, showed 1.7-fold greater function in vitamin D-dependent transcriptional activation of a reporter through the regulation of a vitamin D response element [22]. The FokI rs2228570 polymorphism is the only VDR gene polymorphism involved in the generation of altered protein expression [12]. Apart from obesity and insulin resistance, complex genetic (ethnicity) and non-genetic (epigenetic) mechanisms may have a role in the etiology of GDM [9].

The cross-sectional design, small sample size, and absence of postpartum follow-up are the limitations of this study.

**Conclusion**

This study showed that VDR gene FokI SNPs were independently associated with an increased risk of GDM in Turkish pregnant women. VDR gene FokI SNPs may be considered as a risk factor for metabolic disorders in GDM. VDR FokI SNPs may have a role in the etiology of GDM. Further studies in different populations are needed to confirm these results.
Abbreviations
25(OH) vitamin D3; 25-hydroxyvitamin D3; BMI: body mass index; BP: blood pressure; GDM: gestational diabetes mellitus; HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment-insulin resistance index; LD: Pair-wise linkage disequilibrium

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors’ contributions
MA and SB, contributions to conception and design, or acquisition of data, or analysis and interpretation of data, involved in drafting the manuscript and approved the final manuscript; FAP, NE, MU, MK, OO and MC contributed to conception and design, or acquisition of data, or analysis and interpretation of data and approved the final manuscript; EC, revising it critically for important intellectual content; and have given final approval of the version to be published.

Ethics approval and consent to participate
This retrospective study was approved by Diskapi Yildirim Beyazit Teaching and Research Hospital Ethics Board (Number.26.02.2015) and written consent was obtained from the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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