LEVEL OF BIOCHEMICAL PARAMETERS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS DEPENDING ON THE GENOTYPE OF THE FOKI POLYMORPHISM IN THE VITAMIN D3 RECEPTOR (VDR GENE)

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SUMMARY

Objectives: Diabetes mellitus type 2 (T2DM) is a multifactorial and polygenic disorder characterised by chronic hyperglycaemia accompanied by impaired lipid, carbohydrate, and protein metabolism. The disease is associated with several genetic polymorphisms, including the FokI polymorphism in the vitamin D receptor (VDR) gene.

Methods: We conducted a study of 327 probands (191 T2DM patients, 136 controls), with a mean age 65.06 (SD ± 10.88) years of patients with T2DM and 58.89 (SD ± 6.59) years in the healthy probands. We investigated the association between FokI polymorphism and biochemical parameters in T2DM patients in the Slovak population. Anthropometric measurements, biochemical, and genetic analysis were statistically evaluated by Statistica ver.13 software using t-tests.

Results: Biochemical analysis confirmed significantly higher mean values of total cholesterol (TC), triglyceride (TG), glucose (GLU), and uric acid (UA) ($p < 0.001$) in T2DM probands and statistically significantly lower values of high-density lipoprotein (HDL), cholesterol and vitamin D ($p < 0.001$). Allele frequencies and genotype distributions of the FokI (rs2228570) polymorphism were not significantly different between T2DM patients and controls ($p = 0.909$). Patients with T2DM and TT genotype had the highest glucose level of 11.39 (SD ± 2.32) uU/ml ($p < 0.001$).

Conclusion: Our study did not provide evidence for an association of the investigated FokI polymorphism of the VDR gene with T2DM in the Slovak population. Further research is needed to evaluate the impact of single nucleotide polymorphisms (SNPs) in the VDR gene, focusing on related genetic analyses in a larger T2DM cohort.

Key words: T2DM, glucose, SNP FokI, HDL, vitamin D receptor

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https://doi.org/10.21101/cejph.a7837

INTRODUCTION

Diabetes mellitus type 2 (T2DM) is a metabolic disease characterised by chronic hyperglycaemia accompanied by impaired lipid, carbohydrate, and protein metabolism. Obesity and impaired glucose tolerance are important risk factors for the development of this type (1). T2DM is associated with abnormalities in plasma lipids and lipoproteins, including reduced high-density lipoprotein (HDL) cholesterol, a predominance of small dense low-density lipoprotein (LDL) cholesterol particles, and high triglyceride (TG) levels. These abnormalities occur in many patients despite normal LDL cholesterol levels (2).

These changes are also a major feature of the insulin resistance syndrome that underlies many cases of T2DM. Individuals with diabetes often exhibit a variety of lipid risk factors that include higher levels of total cholesterol (TC), LDL, and TG, as well as lower levels of HDL (3, 4). Insulin resistance plays an important role in the development of T2DM, and the pathogenesis of T2DM is generally considered to be the result of interactions between multiple genes as well as gene-environment interactions (5). Many genes, such as the vitamin D receptor (VDR) gene, are involved in the development of T2DM in different populations. Vitamin D is considered an important factor in reducing the risk of T1DM and T2DM (6).

Its mechanism of action involves a direct effect via nuclear VDR receptors on genes encoding proteins related to normal B-cell function and genes encoding proteins affecting immune mechanisms, as well as mechanisms of insulin resistance.

Vitamin D also directly and indirectly influences calcium metabolism, thereby interfering with the regulatory processes of insulin secretion and action (7). Previous studies have shown that serum vitamin D levels are associated with type 2 diabetes in adults. Low blood levels of 25(OH)D are a possible risk factor for the development of type 2 diabetes. Beta-cell dysfunction and insulin resistance have been reported in individuals with low serum 25(OH)D levels. Studies have shown that vitamin D deficiency reduces glucose tolerance and inhibits insulin secretion (8). Variations in gene sequences, such as single nucleotide polymorphisms (SNPs), explain individual differences in traits such as susceptibility to disease, abnormal levels of biochemical markers, or response to treatment.

Candidate genes for T2DM risk present in specific parts of the genome are classified as those involved in disease onset, related pathways, and functions. The VDR gene is localised on chromosome 12q12-q14 9. Several VDR variants were observed; ApaI (rs7975232), BsmI (rs1544410), EcoRV, TaqI (rs731236), Tru9I, FokI (rs2228570), and CDX2 in association with T2DM.

FokI is located in exon 2 of the DNA gene segment and near the promoter at the 5' end of the gene (9). Several studies confirm the relationship between FokI polymorphism and obesity (10).

However, the relationship between the FokI polymorphism of the VDR gene, obesity, and diabetes is controversial, and more randomized clinical trials are needed.

MATERIALS AND METHODS

A total of 327 individuals were included in the study. T2DM was diagnosed in 191 patients with a mean age of 65.06 (SD ± 10.88) years. The control group consisted of 136 disease-free individuals with a mean age of 58.89 (SD ± 6.59) years. Biological material (blood) was obtained in cooperation with a diabetology outpatient clinic in eastern Slovakia. Study participants were asked to sign an informed consent form. Anthropometric measurements included body height (cm) and body weight (kg) to calculate BMI (kg/m^2). The normal BMI ranges from 19–25 (kg/m^2). A BMI value higher than the range of 25–29.90 was considered overweight, and a value of 30–34.90 was considered grade 1 obese. Body weight and body height measurements were taken without shoes and participants wore light clothing.

This measurement was recorded to an accuracy of 0.1 kg by a SECA 700 (Seca GmbH & Co. KG., Germany). The blood samples of 10 ml were collected from patients into Vacutainer tubes containing EDTA. They were centrifuged for 10 min at 15,000 rpm for serum extraction.

The Cobas Integra 400 Plus biochemical analyser (Roche, Germany) was used to analyse the biochemical parameters triglyceride (TG), serum glucose (GLU), and lipid profile – including total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, uric acid (UA), and vitamin D (vitD). Blood samples of 7.5 ml were collected from patients into Vacutainer tubes without anticoagulants. The ReliaPrep™ Blood gDNA Miniprep System (Thermo Fisher, USA) was used to extract genomic DNA from blood according to the manufacturer's instructions.

The NanoDrop™ 2000 UV-VIS spectrophotometer was used to determine DNA concentration and purity. Genotyping was performed according to the manufacturer's protocols. The FokI SNP (rs2228570) was evaluated using a pre-designed TaqMan genotyping assay from Applied Biosystems, USA (assay ID: C_12060045_20). Amplification and detection were performed in 96-well PCR plates using the StepOne™ Real-Time PCR System (Applied Biosystems, USA).

After PCR was completed, allelic discrimination was analysed using StepOne™ software (Applied Biosystems, USA). Statistical analyses for all clinical and laboratory variables were performed using Statistica v.12 software. Continuous data are presented as mean ± SD; statistical differences in levels were assessed using two-sided t-tests for independent samples.

Pearson's χ^2 test was used for percentage data. Differences in variables between genotypes were compared using analysis of variance (ANOVA).

RESULTS

The basic clinical characteristics of 327 probands (136 control probands and 191 subjects with T2DM) are shown in Table 1. The mean age of the control group was 58.89 (SD ± 6.59) years, mean BMI was 25.35 (SD ± 4.05) kg/m^2. Mean glucose 4.57 (SD ± 0.68) mmol/L, total cholesterol 4.54 (SD ± 0.92) mmol/L, HDL cholesterol 1.56 (SD ± 0.44) mmol/L, LDL cholesterol 3.18 (SD ± 0.86) mmol/L, mean TG level 1.36 (SD ± 0.68) mmol/L, UA level 263.68 (SD ± 42.12) μmol/L, and mean vitamin D level 67.99 (SD ± 15.37) nmol/L. The T2DM cohort consisted of 191 probands with a mean age of 65.06 (SD ± 10.88) years. The BMI value of 31.04 (SD ± 4.21) kg/m^2 was significantly higher in probands with the disease compared to controls. Glucose levels were also statistically significantly higher at 7.56 (SD ± 2.54) mmol/L, $p < 0.001$; total cholesterol 4.81 (SD ± 1.03) mmol/L, $p = 0.015$; HDL cholesterol 1.25 (SD ± 0.30) mmol/L, $p < 0.001$; LDL cholesterol 3.04 (SD ± 0.84) mmol/L, $p = 0.137$; TG level 2.17 (SD ± 1.27) mmol/L, $p < 0.001$; mean UA level 316.91 (SD ± 85.29) μmol/L, $p < 0.001$; and mean vitamin D level 34.15 (SD ± 14.90) nmol/L, $p < 0.001$.

The distribution of alleles and genotypes of the FokI (rs2228570) VDR gene polymorphism is summarized in Table 2. The FokI VDR gene polymorphism was in Hardy-Weinberg equilibrium in controls ($p = 0.212$) and probands with T2DM ($p = 0.264$). SNP allele frequency was not statistically significant between groups ($p = 0.909$, OR = 1.012, 95% CI: 0.742–1.934).

The effect of FokI (rs2228570) VDR gene polymorphism on the level of biochemical parameters depending on genotypes between controls and probands with T2DM is shown in Table 3.

Patients with T2DM and CC genotype had significantly higher BMI (T2DM 30.69 ± 4.49 kg/m^2, controls 26.15 ± 3.55 kg/m^2), TG (T2DM 2.03 ± 1.10 mmol/L, controls 1. 52 ± 0.78 mmol/L, $p = 0.005$), GLU (T2DM 5.92 ± 1.59 uU/ml, controls 4.63 ± 0.75 uU/ml, $p < 0.001$), and UA (T2DM 326.76 ± 82.35 μmol/L, controls 261.95 ± 47.03 μmol/L, $p < 0.001$).

HDL cholesterol (T2DM 1.27 ± 0.30 mmol/L, controls 1.59 ± 0.54 mmol/L; $p < 0.001$) and vitD (T2DM 35.18 ± 15.97 nmol/L, controls 70.10 ± 15.27 nmol/L, $p < 0.001$) levels were significantly lower. The values of TC ($p = 0.377$) and LDL cholesterol ($p = 0.092$) were not statistically significant. Patients with T2DM and CT genotype had significantly higher BMI (T2DM

Table 1. *Comparison of anthropological and biochemical parameters between T2DM patients and controls*

Parameter	T2DM n = 191 Mean (SD)	Controls n = 136 Mean (SD)	p-value
Age (years)	65.06 (10.88)	58.89 (6.59)	**< 0.001**
Body height (m)	170.27 (8.85)	167.98 (10.04)	0.029
Body weight (kg)	90.08 (14.34)	71.41 (11.86)	**< 0.001**
BMI (kg/m^2)	31.04 (4.21)	25.35 (4.05)	**< 0.001**
TC (mmol/L)	4.81 (1.03)	4.54 (0.92)	0.015
HDL (mmol/L)	1.25 (0.30)	1.56 (0.44)	**< 0.001**
LDL (mmol/L)	3.04 (0.84)	3.18 (0.86)	0.137
TG (mmol/L)	2.17 (1.27)	1.36 (0.68)	**< 0.001**
GLU (uU/ml)	7.56 (2.54)	4.57 (0.68)	**< 0.001**
UA (μmol/L)	316.91 (85.29)	263.68 (42.12)	**< 0.001**
VitD (nmol/L)	34.15 (14.90)	67.99 (15.37)	**< 0.001**

BMI – body mass index; TC – total cholesterol; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein; TG – triglycerides; GLU – glucose; UA – urea acid; VitD – vitamin D; SD – standard deviation; statistical significance p < 0.001

Table 2. *Frequency of alleles and genotypes of SNP FokI between cases and control*

rs2228570	T2DM n = 191	Controls n = 136
CC	70	50
CT	85	59
TT	36	27
f (C)	0.58	0.58
f (T)	0.41	0.41
HWE	0.264	0.212
OR	1.018	
χ^2	1.248	
p-value	0.909	

T2DM – patients with diabetes mellitus type 2; CC – homozygous genotype; CT – heterozygous genotype; TT– homozygous genotype; f (C) – frequency of allele C; f (T) – frequency of allele T; HWE – Hardy-Weinberg equilibrium; OR – risk rate; χ^2 – chi-square test

31.63 ± 3.84 kg/m^2, controls 24.89 ± 3.72 kg/m^2, p < 0.001), TG (T2DM 2.18 ± 1.18 mmol/L, controls 1.37 ± 0.52 mmol/L, p < 0.001), GLU (T2DM 7.29 ± 1.29 uU/mL, controls 4.53 ± 0.65 uU/mL, p < 0.001), UA (T2DM 319.74 ± 89.65 μmol/L, controls 261.65 ± 42.84 μmol/L, p < 0.001).

HDL cholesterol (T2DM 1.22 ± 0.28 mmol/L, controls 1.52 ± 0.33 mmol/L; p < 0.001) and vitD (T2DM 33.28 ± 14.57 nmol/L, controls 65.25 ± 16.01 nmol/L, p < 0.001) were significantly lower. TC (p = 0.128) and LDL cholesterol (p = 0.496) values were not statistically significant.

Patients with T2DM and TT genotype had higher BMI (T2DM 30.33 ± 4.38 kg/m^2, controls 26.99 ± 4.07 kg/m^2, p < 0.01), TG (T2DM 2.44 ± 1.70 mmol/L, controls 1.47 ± 0.70 mmol/L, p < 0.01), and GLU (T2DM 11.39 ± 2.32 uU/ml, controls 4.56 ± 0.59 uU/ml, p < 0.001). HDL cholesterol (T2DM 1.26 ± 0.35 mmol/L, controls 1.58 ± 0.46 mmol/L; p < 0.01) and vitD (T2DM 34.21 ± 13.78 nmol/L, controls 70.07 ± 13.65 nmol/L, p < 0.001) were statistically significantly lower. Levels of TC (p = 0.056), LDL cholesterol (p = 0.927) and UA (p = 0.212) were not statistically significant.

When comparing the levels of biochemical parameters TC (p = 0.949), HDL (p = 0.528), LDL (p = 0.089), TG (p = 0.308), UA (p = 0.114), and VitD (p = 0.735) according to genotypes in the set of patients with T2DM, no significant differences were found.

A statistically significant difference (p < 0.001) was observed in GLU levels between the genotypes, CC (5.92 ± 1.59 uU/ml), CT (7.29 ± 1.29 uU/ml), and TT (11.39 ± 2.32 uU/ml) genotypes. The comparison of biochemical parameters among CC, CT, and TT genotypes in the T2DM patient group is shown in Table 4.

DISCUSSION

The VDR gene is considered a pleiotropic gene and is a transcription factor that mediates the action of vitamin D3 by controlling the expression of hormone-sensitive genes (11). Dysfunction of the VDR gene can lead to insulin resistance (12). In this study, we investigated the effect of genotypes of FokI polymorphism of the VDR gene on biochemical parameters in a sample of patients with T2DM in the Slovak population. The role of vitamin D in the pathogenesis and prevention of T2DM has generated various debates. Several observational studies have reported a correlation between VDR gene polymorphisms and T2DM and identified important relationships between vitamin D deficiency, obesity, and diabetes (13, 14).

These three factors can strongly influence each other. Vitamin D deficiency can lead to obesity and chronic diseases such as type 2 diabetes, cardiovascular disease, etc.

The VDR gene is located on chromosome 12q13.17 and contains 11 exons. Several polymorphisms in the VDR gene have been identified and their functional significance and predisposition to disease have been investigated (15, 16). The FokI polymorphism (rs2228570) localized in exon 2 is the only known locus affecting the structure of the produced VDR protein.

Table 3. *Comparison of biochemical parameters between genotypes CC, CT and TT by controls group and T2DM patients*

	T2DM n = 70 Mean (SD)	**Controls n = 50 Mean (SD)**	**p-value**
Genotype CC			
Age (years)	66.11 (10.29)	53.46 (17.98)	**0.001**
Body weight (kg)	87.78 (13.31)	76.13 (15.57)	**< 0.001**
BMI (kg/m^2)	30.69 (4.49)	26.15 (3.55)	**< 0.001**
TC (mmol/L)	4.70 (1.06)	4.53 (0.970)	0.377
HDL (mmol/L)	1.27 (0.30)	1.59 (0.54)	**< 0.001**
LDL (mmol/L)	2.88 (0.82)	3.14 (0.84)	0.092
TG (mmol/L)	2.03 (1.10)	1.52 (0.78)	**0.005**
GLU (uU/ml)	5.92 ± 1.59	4.63 (0.75)	**< 0.001**
UA (µmol/L)	326.76 (82.35)	261.95 (47.03)	**< 0.001**
VitD (nmol/L)	35.18 (15.97)	70.10 (15.27)	**< 0.001**
	T2DM n = 85 Mean (SD)	**Controls n = 59 Mean (SD)**	**p-value**
Genotype CT			
Age (years)	65.48 (10.64)	57.57 (5.983)	**< 0.001**
Body weight (kg)	92.87 (15.06)	70.79 (11.25)	**< 0.001**
BMI (kg/m^2)	31.63 (3.84)	24.89 (3.72)	**< 0.001**
TC (mmol/L)	4.89 (0.95)	4.65 (0.88)	0.128
HDL (mmol/L)	1.22 (0.28)	1.52 (0.33)	**< 0.001**
LDL (mmol/L)	3.09 (0.78)	3.19 (0.85)	0.496
TG (mmol/L)	2.18 (1.18)	1.37 (0.52)	**< 0.001**
GLU (uU/ml)	7.29 (1.29)	4.53 (0.65)	**< 0.001**
UA (µmol/L)	319.74 (89.65)	261.65 (42.84)	**< 0.001**
VitD (nmol/L)	33.28 (14.57)	65.25 (16.01)	**< 0.001**
	T2DM n = 36 Mean (SD)	**Controls n = 27 Mean (SD)**	**p-value**
Genotype TT			
Age (years)	62.02 (12.26)	58.96 (6.16)	0.238
Body weight (kg)	88.00 (13.74)	76.48 (11.93)	**< 0.001**
BMI (kg/m^2)	30.33 (4.38)	26.99 (4.07)	**< 0.01**
TC (mmol/L)	4.87 (1.16)	4.34 (0.92)	0.056
HDL (mmol/L)	1.26 (0.35)	1.58 (0.46)	**< 0.01**
LDL (mmol/L)	3.23 (0.96)	3.25 (0.97)	0.927
TG (mmol/L)	2.44 (1.70)	1.47 (0.70)	**< 0.01**
GLU (uU/ml)	11.39 (2.32)	4.56 (0.59)	**< 0.001**
UA (µmol/L)	291.05 (77.01)	271.33 (29.53)	0.212
VitD (nmol/L)	34.21 (13.78)	70.07 (13.65)	**< 0.001**

BMI – body mass index; TC – total cholesterol; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein; TG – triglycerides; GLU – glucose; UA – urea acid; VitD – vitamin D; SD – standard deviation; statistical significance p < 0.001

The T allele encodes a protein with 427 amino acids and the C allele encodes a protein with 424 amino acids. The shorter variant of the VDR protein is thought to function more efficiently and increase the ability to bind 1,25-dihydroxyvitamin D12. Rela-

Table 4. *Comparison of biochemical parameters between genotypes CC, CT and TT in group of patients with T2DM*

	T2DM n = 53 Mean (SD)	T2DM n = 67 Mean (SD)	T2DM n = 41 Mean (SD)	p-value
	CC	CT	TT	
Age (years)	66.11 (10.29)	65.48 (10.64)	62.02 (12.26)	0.167
Body weight (kg)	87.78 (13.31)	92.87 (15.06)	88.00 (13.74)	0.055
BMI (kg/m^2)	30.69 (4.49)	31.63 (3.84)	30.33 (4.38)	0.204
TC (mmol/L)	4.70 (1.06)	4.89 (0.95)	4.87 (1.16)	0.494
HDL (mmol/L)	1.27 (0.30)	1.22 (0.28)	1.26 (0.35)	0.528
LDL (mmol/L)	2.88 (0.82)	3.09 (0.78)	3.23 (0.96)	0.089
TG (mmol/L)	2.03 (1.10)	2.18 (1.18)	2.44 (1.70)	0.308
GLU (uU/ml)	5.92 (1.59)	7.29 (1.29)	11.39 (2.32)	**< 0.001**
UA (μmol/L)	326.76 (82.35)	319.74 (89.65)	291.05 (77.01)	0.114
VitD (nmol/L)	35.18 (15.97)	33.28 (14.57)	34.21 (13.72)	0.735

BMI – body mass index; TC – total cholesterol; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein; TG – triglycerides; GLU – glucose; UA – urea acid; VitD – vitamin D; SD – standard deviation; statistical significance p < 0.001

tively higher levels of vitamin D may reduce the risk of T2DM by increasing pancreatic b-cell secretory function and improving insulin resistance. This biological mechanism could explain the association between the T allele of the FokI polymorphism and susceptibility to T2DM (17). In our study, significantly lower ($p < 0.001$) vitamin D levels were observed in T2DM patients at 34.15 (SD ± 14.90) nmol/L compared to healthy probands at 67.99 (SD ± 15.37) nmol/L. Several studies have reported a high prevalence of hypovitaminosis D in patients with T2DM in different populations (18, 19).

Significant statistical differences were observed in increased BMI ($p < 0.001$), TG ($p < 0.001$), TC ($p = 0.015$), GLU ($p < 0.001$), and UA ($p < 0.001$) in patients with T2DM.

In contrast, lower HDL values ($p < 0.001$) were achieved by T2DM patients similar to the studies by Mahjoubi et al. and Al-Darraji et al. (20, 21). We evaluated the FokI polymorphism and its corresponding CC, CT, and TT genotypes in relation to the disease.

The FokI polymorphism in the VDR gene was not associated with T2DM in the Slovak population. The frequency of the T allele in the FokI polymorphism was the same in T2DM patients f(T) = 0.41 and healthy probands f(T) = 0.41.

Our findings are also consistent with those of several authors (22, 23). Nevertheless, Rawoof et al. reported that T2DM patients had a higher genotypic and allelic frequency of FokI polymorphism (C>T; $p < 0.001$), and that the f(T) allele is a risk factor for T2DM for the Kashmiri population (24). Alfaqih et al. (10) showed by analysis that the frequency of the C allele was higher in T2DM patients than in controls, whereas the frequency of the T allele was lower ($p = 0.039$). These results suggest that the C allele (rs2228570) may be a high-risk allele for T2DM in the Jordanian population. Our findings are also inconsistent with the conclusions of the study by Angel et al. (18), who found that the C allele of the FokI polymorphism is a high-risk allele for T2DM in the Chilean population. A study by Safar et al. demonstrated that the C allele has a significant association with the risk of T2DM in an Emirati population (25). Nor is this finding consistent with our conclusion. The effect of CC, CT, and TT genotypes on the levels of biochemical parameters was statistically significant only in the case of glucose levels ($p < 0.001$). Diabetics with TT genotype had the highest glucose level of 11.39 (SD ± 2.32) uU/ml.

Although the effects of this polymorphism in relation to glucose metabolism have been investigated from several perspectives, our results are consistent with similar previously published data. Mackawy and Badawi (22) and Schuch et al. (26) found a significant association between the T allele and fasting insulin resistance in Egyptian and Brazilian adults.

The FokI polymorphism in a meta-analysis published by Li et al. was associated with an overall significantly increased risk of T2DM (T vs. C: OR = 1.25, 95% CI: 1.10–1.41; extreme model TT vs. CC: OR = 1.48, 95% CI: 1.13–1.94; recessive model TT vs. CT + CC: OR = 1.51, 95% CI: 1.25–1.82). This meta-analysis suggests that the FokI polymorphism of the VDR gene could be a risk factor for T2DM, particularly in the Asian population (27).

Numerous original studies and 4 published meta-analyses have reported an association between vitamin D receptor polymorphisms (BsmI, FokI, ApaI and TaqI) and the risk of T2DM. Therefore, an updated meta-analysis was performed to further investigate these issues. Overall, the VDR FokI polymorphism was associated with a significantly reduced risk of T2DM in African and Asian countries (28).

This case-control study showed that the VDR gene FokI SNP was not associated with T2DM in the Slovak population. The frequency of FokI polymorphism alleles was not different in T2DM patients compared to controls. The level of biochemical parameters except glucose level was not affected by genotype.

CONCLUSION

Our results showed that the FokI polymorphism of the VDR gene was not associated with the risk of T2DM in the Slovak population. The value of analyzed biochemical parameters (TC, TG, HDL, LDL, UA, vitD) was not influenced by the genotype (CC, CT, and TT) of FokI polymorphism. The exception was the glucose level in T2DM patients with the TT genotype, where the

level was the highest. The presence of the TT genotype in patients with T2DM may indicate a possible risk of impaired glucose metabolism. The effect of the FokI polymorphism on the risk of T2DM may be specific to certain ethnic populations through interaction with other environmental and clinical factors. We anticipate that further studies in different European populations are largely needed to fully elucidate differences in susceptibility to T2DM in the FokI polymorphism.

Acknowledgement

This work was supported by KEGA project No. 002PU-4/2021 and VEGA project No. 1/0069/22.

Conflicts of Interest

None declared

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Received April 12, 2023
Accepted in revised form October 11, 2023