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C/T polymorphism of the rs7903146 nucleotide of the *TCF7L2* gene and the risk of developing diabetes mellitus type 2

ABSTRACT

Background. The continuously increasing incidence of type 2 diabetes mellitus (DMt2) is an important problem in current medicine. In addition to well-known environmental factors that may contribute to this disease, genetic factors may also play a role. One of the genes that may be responsible for an increased risk of DMt2 development is the transcription factor *TCF7L2* gene. This work was aimed to assess a correlation between the rs7903146 polymorphism in the *TCF7L2* gene and age at DMt2 diagnosis, presence of obesity, arterial hypertension, and time elapsed from DMt2 diagnosis to the start of insulin therapy.

Methods. An analysis of the studied polymorphism was performed in 282 patients diagnosed with DMt2. Patients were divided into groups depending on the age of the onset of DMt2: group A (n = 82) — DMt2 diagnosis below the age of 40 years, group B (n = 100) — DMt2 diagnosis between the ages of 40 and 60 years, group C (n = 100) — DMt2 diagnosis above the age of 60 years.

Results. In group C, there was a significantly lower number of patients with a TT genotype of the studied polymorphism compared to the combined group A + B ($P < 0.05$).

Conclusions. There is a correlation between the rs7903146 polymorphism in the *TCF7L2* gene and age at DMt2 diagnosis. No correlation has been demonstrated between the studied polymorphism and the presence of obesity, arterial hypertension, and time elapsed from DMt2 diagnosis to the start of insulin therapy. (Clin Diabetol 2020; 9; 4: 212–218)

Key words: diabetes type 2, *TCF7L2* gene, age, polymorphism

Introduction

The continuously increasing incidence of type 2 diabetes mellitus (DMt2), spanning all age groups, which is currently estimated at approximately 8%, classifies DMt2 as the most common social disease. The incidence of diabetes in the Polish population is comparable to the average values observed worldwide [1]. The most numerous population of patients with diabetes are people aged 40 to 59 years. In the pathogenesis of DMt2, in addition to known environmental factors, genetic factors which have been extensively studied for several years play a role. The genome-wide association study (GWAS) has identified more than 60 loci related to a different degree with the risk of DMt2 development, mainly due to the effect on pancreatic beta cell function, insulin resistance and obesity [2]. The most well-known gene that can contribute to DMt2 development is the transcription factor 7-like

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2 gene (TCF7L2). The association of polymorphism in this gene with DMt2 development has been demonstrated for the first time in an Icelandic population in 2006 [3]. In subsequent studies, this relationship was confirmed in various ethnic groups [4–9]. The strongest association with the risk of developing DMt2 has been demonstrated for the T allele of the rs7903146 polymorphism in this gene. The odds ratio of DMt2 development in carriers of a single T allele is about 1.4, while in people with TT genotype, the chance of DMt2 development is about twice as high as in people without an unfavorable allele [10].

The product of the TCF7L2 gene is the TCF7L2 transcription factor, an important element of the intracellular WNT signaling pathway which plays an important role in many basic physiological processes such as embryonic development, stem cell maintenance, cell proliferation and migration, and oncogenesis [11]. While unfavorable polymorphisms of the TCF7L2 gene in many studies have been associated with a higher risk of DMt2, a similar relationship has not been shown for type 1 diabetes, maturity onset diabetes of the young (MODY type diabetes), and persistent diabetes in newborns [12, 13]. Nevertheless, there was a significant correlation between the rs7903146 polymorphism in the *TCF7L2* gene and the risk of latent autoimmune diabetes in adults (LADA) [12, 14]. Other polymorphisms of this gene were associated with an increased risk of gestational diabetes [15, 16]. In many studies, reduced insulin secretion was demonstrated in carriers of the T allele of rs7903146 polymorphism in the *TCF7L2* gene both in diabetic patients and in healthy subjects, which was also associated with a higher risk of DMt2 development [17–19]. The unfavorable polymorphism in the *TCF7L2* gene leads to impaired conversion of proinsulin to insulin, which most probably results from the regulating effect of TCF7L2 on the expression of the genes for convertase 1 and 2, responsible for this conversion [20, 21]. The *TCF7L2* gene polymorphism may also affect carbohydrate metabolism by affecting the incretin system. It has been shown that the production process as well as the mechanism of action of glucagon-like peptide 1 (GLP-1) are largely regulated by the WNT signaling pathway [22]. Since the TCF7L2 transcription factor gene is expressed not only in pancreatic and intestinal cells, but also in the liver, brain, skeletal muscle, adipose tissue, and bones, the effect of this gene's polymorphism on carbohydrate metabolism may include various pathophysiological pathways leading to the development of DMt2.

The influence of genetic factors on the age of patients in which DMt2 is diagnosed is not well understood. The relation between TCF7L2 polymorphism and the presence of hypertension or obesity also remains inconclusive, which additionally increases the risk of adverse cardiovascular events. Since the time from the diagnosis of the disease to the implementation of insulin therapy varies between patients, an interesting issue seems to be the assessment of the impact of genetic factors on the above-mentioned period, which indirectly reflects the time from the onset of the disease to the failure of beta cells. Due to a number of doubts regarding the influence of genetic factors on the development and progression of DMt2, the aim of this study is to evaluate the association of the rs7903146 polymorphism in the *TCF7L2* gene with:

— the age at DMt2 diagnosis;
— co-existence of hypertension and obesity in patients with DMt2 diagnosed in various age groups;
— a period of insulin independence.

Methods

The study included 282 patients with DMt2. Patients were divided into three groups depending on the age of the patients in which DMt2 was diagnosed:

— group A (n = 82) patients with DMt2 diagnosed before or at the age of 40 years;
— group B (n = 100) patients with DMt2 diagnosed between the ages of 40–60 years;
— group C (n = 100) patients with DMt2 diagnosed at or after the age of 60 years.

The inclusion criterion was:

— age ≥ 35 years, and
— effective treatment with diet or oral drugs/insulin ≥ 6 months.

The exclusion criterion was difficult logical contact with the patient.

After receiving written informed consent to participate in the study, a 4.9 ml blood sample was collected from each patient from the ulnar vein into S-Monovette test tubes (Sarstedt) containing 6.4 mg of potassium edetate. After 30 minutes from the time of collecting the biological material, the test tubes with blood were centrifuged (3,000 rpm, 10 min) and then stored at –20°C until DNA isolation, no longer than 6 months. Polymerase chain reaction (PCR) and allele identification were performed on a 7300 Real Time PCR System (Applied Biosystems). Genotyping of the C/T polymorphism of single nucleotide rs7903146 of the TCF7L2 gene was performed with fluorescence-labeled probes using TaqManPre-designed SNP Genotyping Assay (Applied Biosystems).

All results obtained were subjected to statistical analysis using the software package Statistica 9.0. Continuous parameters were expressed as means with standard deviation (SD), and categorical variables were presented as numbers and percentages. Normality of

Table 1. General characteristics of the studied population

	Group A (n = 82)	Group B (n = 100)	Group C (n = 100)
Age, years (SD)[1]	54.2 (11.5)	62.5 (8.6)	73.8 (7.3)
Gender M/F[2]	48/34	60/40	38/62
Age at diagnosis of DMt2 (SD)[1]	36.9 (4.5)	51.0 (4.7)	67.5 (6.1)
Duration of DMt2, years (SD)[1]	17.4 (11.0)	11.6 (8.0)	6.3 (5.6)
BMI [kg/m^2] (SD)[2]	31.5 (5.2)	30.7 (5.0)	29.0 (4.4)
Waist circumference [cm] (SD)[3]	109.0 (12.0)	106.5 (12.3)	104.3 (12.4)
Arterial hypertension [n (%)]	59 (72%)	75 (75%)	74 (74%)
Dyslipidemia [n (%)]	39 (48%)	61 (61%)	56 (56%)

SD — standard deviation; M/F — male/female; DMt2 — type 2 diabetes mellitus; BMI — body mass index
[1]Between each group, P < 0.05; [2]group C *vs.* group A and group B, P < 0.05; [3]group A *vs.* group C, P < 0.05

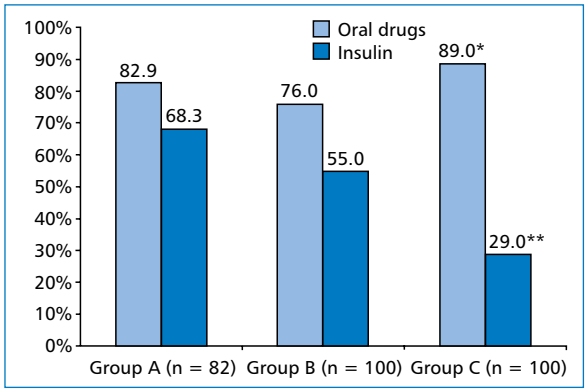

Figure 1. Method of therapy in individual study groups. *Group C *vs.* group B, P = 0.026; **group C *vs.* group B and group A, P < 0.001

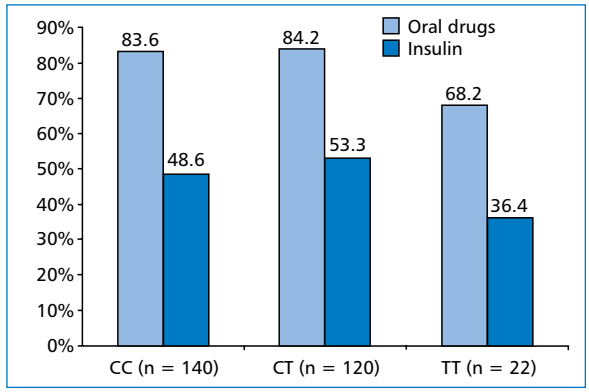

Figure 2. Method of therapy in the carriers of particular genotypes in the entire study population. For all P = NS

data distribution was tested with Shapiro-Wilk test. Comparative analysis between groups was performed using the t-Student test for continuous variables and the χ^2 for dichotomous parameters. P values < 0.05 were considered statistically significant.

The study design received a positive opinion from the Bioethical Committee of the Medical University of Silesia in Katowice.

Results

The general characteristics of the studied population divided into three analyzed groups are presented in Table 1.

Figure 1 shows the mode of therapy in individual groups divided into oral drugs and/or insulin. Statistical analysis showed that in group C, insulin therapy was statistically less frequently used than in other groups (P < 0.001) and oral therapy was more often used than in group B (P = 0.026).

A similar analysis regarding the method of therapy was carried out in relation to patients who are carriers of particular genotypes. In this analysis, there was no statistically significant difference in the mode of therapy between the CC, CT, and TT genotypes (Fig. 2). Similar results were obtained in individual groups A, B, and C.

Table 2. Frequency of particular genotypes in each study group

Group	CC	CT	TT
Group A (n = 82)	37 (45.1%)	35 (42.7%)	10 (12.2%)
Group B (n = 100)	45 (45%)	46 (46%)	9 (9%)
Group C (n = 100)	58 (58%)	39 (39%)	3 (3%)

Table 2 presents the frequency of individual genotypes in the studied groups. The rarest genotype in all studied groups was the TT genotype.

An additional analysis was made for the A + B and B + C combined groups and the frequency of occurrence of particular genotypes was compared to the remaining group. There was no statistical difference in the frequency of particular genotypes between the B + C

Table 3. Frequency of particular genotypes (group A *vs.* group B + C)

Group	CC	CT	TT
Group A (n = 82)	37 (45.1%)	35 (42.7%)	10 (12.2%)
Group B + C (n = 200)	103 (51.5%)	85 (42.5%)	12 (6.0%)

Table 4. Frequency of particular genotypes (group A + B *vs.* group C)

Group	CC	CT	TT
Group A + B (n = 182)	82 (45.1%)	81 (44.5%)	19 (10.4%)
Group C (n = 100)	58 (58.0%)[1]	39 (39.0%)	3 (3.0%)[2]

[1]*vs.* group A + B, P = 0.051; [2]*vs.* group A + B, P = 0.047

combined group and the A group (Table 3). Table 4 presents the frequency of individual genotypes in the A + B combined group compared to the C group. In the C group, a significantly lower percentage of subjects with the TT genotype was found compared to the A + B combined group (3.0% *vs.* 10.4%, P = 0.047). There was also a tendency for the CC genotype to be more frequent in group C compared to the combined group A + B (58.0% *vs.* 45.1%, P = 0.051).

In the analysis of the percentage of patients with the CC genotype compared to patients who were carriers of at least one T allele, no statistically significant differences were found between the studied groups.

In a similar analysis comparing the A + B combined group and the C group, a trend towards a less frequent genotype with at least one T allele in the C group than in the A + B combined group was demonstrated (42.0% *vs.* 54.9%, P = 0.051). There was no significant difference in the frequency of individual genotypes between the B + C combined group and the A group.

In the studied groups, there was no difference in the mean body mass index (BMI) among the carriers of individual genotypes. An additional analysis of the percentage of overweight and/or obese patients in individual groups did not show any relation to the studied polymorphism.

The CC and CT genotype carriers showed significantly lower BMI [kg/m^2] in group C compared to group A (for CC genotype 29.3 *vs.* 31.5, P < 0.05, for CT genotype 28.6 *vs.* 32.2, P < 0.05) as well as in group C compared to group B (for CC genotype 29.3 *vs.* 31.0, P = 0.05, for CT genotype 28.6 *vs.* 30.7, P = 0.06). This relationship was not found among carriers of the TT genotype.

The mean time from the diagnosis of DMt2 to the implementation of insulin therapy did not differ in the

Table 5. Mean time (SD) from diagnosis of DMt2 to implementation of insulin therapy (in years)

Group	CC	CT	TT
Group A (n = 82)	9.4 (6.8)	12.4 (10.8)	4.8 (8.2)
Group B (n = 100)	8.8 (6.9)	8.4 (8.0)	5.8 (5.7)
Group C (n = 100)	3.3 (4.0)[1]	2.2 (3.6)[1]	–

[1]Compared to group A and group B, P < 0.05

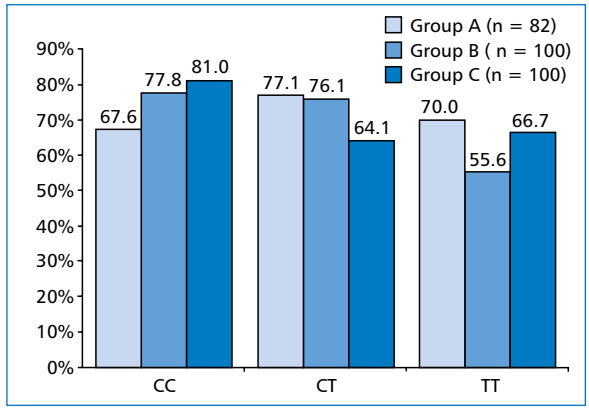

Figure 3. The co-occurrence of hypertension in the study groups

carriers of individual genotypes in each study group. In the carriers of the CC and CT genotype, there was a statistically significantly shorter time from the diagnosis of DMt2 to the implementation of insulin therapy in group C in comparison to both group A and group B (P < 0.05). A similar analysis could not be performed for carriers of the TT genotype due to the fact that there was only one patient in group C with this genotype in whom insulin therapy was used (Table 5).

There was no statistically significant relationship between individual genotypes and the co-occurrence of hypertension in the study groups (Fig. 3).

Discussion

In the presented study, the analysis of the gene polymorphism was performed in the groups of patients differing in the age of DMt2 diagnosis. According to the data of the International Diabetes Federation, the largest group of patients with diabetes are people aged 40 to 59 years. Patients with DMt2 diagnosed in this age range were included in group B, patients with disease diagnosed before this period were included in group A, and patients with disease diagnosed after this period were included in group C. There were 82 patients qualified to group A, 100 patients qualified

to group B, and 100 patients qualified to group C. The lower number of subjects in group A resulted from the lack of a sufficient number of patients diagnosed with DMt2 at or before the age of 40 years at study sites in the planned period, which is associated with the phenotype of DMt2, which in most cases affects people over 40 years of age.

The division of the studied population into the three groups defined above results in some differences in the general characteristics of the population studied. In the group of people diagnosed with DMt2 after the age of 59, a significantly smaller percentage of men was found than in other groups, which probably results from the longer average life expectancy of women in relation to men in the general population. The division of the population used in the study also influenced the average duration of diabetes, which was the longest in patients diagnosed earlier in life, and the shortest in the group of patients diagnosed after the age of 59.

The TCF7L2 transcription factor gene is one of the known candidate genes that may contribute to DMt2 development. The rs7903146 polymorphism of this gene results in the presence of three genotypes in the population: CC, CT, and TT. In all of the studied groups, the smallest percentage of patients were carriers of the TT genotype (from 3% in group C to 12.2% in group A). This result is similar to the data for the Caucasian population, for which the frequencies of particular genotypes are as follows: CC — 54.9%, CT — 34.5%, and TT — 10.6% [23].

The age of DMt2 onset is an important factor affecting the quality and life expectancy of patients. Because the duration of diabetes is directly related to the development of its complications, the diagnosis of the disease at a younger age has an adverse effect on the future fate of these patients. It was shown that patients with early diagnosed diabetes require the implementation of insulin therapy within three months of the diagnosis significantly more often than those diagnosed later in life. In this group of patients, the presence of microalbuminuria was also more frequent [24]. In another study, it was found that in the group of patients with the earlier diagnosis of the disease, the relative risk of macrovascular complications is twice as high as in the group of patients with the later diagnosis of diabetes [25].

Unfavorable genetic factors may be one of the reasons for earlier development of DMt2. In a study on a Mexican-American population, there was no statistical significance regarding the influence of the *TCF7L2* gene polymorphism on the age of onset of DMt2, although a trend towards such dependence was observed ($P = 0.055$). A similar result was obtained for the rs12255372 polymorphism of the *TCF7L2* gene, also considered one of the main genetic factors that may contribute to DMt2 development [26]. In another study on a Caucasian population, a relationship of the unfavorable T allele of the studied polymorphism with the earlier onset of DMt2 was found [27].

In the present study, it was shown that in the group of patients with DMt2 diagnosed before the age of 60 years, the presence of TT genotype is more frequent than in the group of patients with late diagnosis of DMt2. In turn, in the carriers of at least one T allele, a trend towards more frequent occurrence of this allele was demonstrated in the group of patients diagnosed with DMt2 before the age of 60 years. This may indicate an adverse effect of the T allele, and in particular the TT genotype, on the risk of developing diabetes earlier in life.

One of the most common comorbidities among patients with DMt2 is arterial hypertension. In the present study, in all age groups, the proportion of patients with hypertension was over 70% and did not differ significantly between the groups. There was no statistically significant relationship between the occurrence of hypertension and the studied polymorphism. Both DMt2 and arterial hypertension are known risk factors for macro- and microangiopathy, causing increased mortality among these patients. The ultrasound measurement of the intima–media thickness in the common carotid artery is considered to be a marker of subclinical atherosclerosis and can be used for identification of patients who are at increased risk of macroangiopathy, such as stroke or myocardial infarction. Bartman et al. showed that microvascular complications in patients with type 2 diabetes are independently associated with the carotid plaque score but not carotid intima–media thickness. So the study of carotid plaque score may serve to identify patients at risk of microvascular complications in patients with DMt2 [28].

The analysis of the method of therapy in particular groups in this study, including oral drugs and insulin therapy, showed that patients with diabetes diagnosed up to 60 years of age required the implementation of insulin therapy significantly more often than those patients diagnosed at an older age. This fact most probably results from a longer duration of the disease in this group of patients compared to patients diagnosed with DMt2 at older age. In our study, there were no relationships between particular genotypes and the method of therapy in the entire studied population and in individual groups. It was shown that the studied polymorphism had no effect on the mean time from DMt2 diagnosis to the implementation of insulin therapy in all the groups studied. It is worth noting that

in the group of patients diagnosed with DMt2 after the age of 59 years, the average time from diagnosis to implementation of insulin therapy was shorter than in the remaining groups, despite the shortest duration of the disease in this group. This may be due to a natural reduction in pancreatic beta cell function with age. Based on the results of this study, it can be concluded that the late age of diagnosis of DMt2 is associated with the need for earlier implementation of insulin therapy. However, due to the small number of patients treated with insulin in group C, further studies are needed to assess the possible effect of the studied polymorphism on DMt2 treatment.

Obesity is one of the main risk factors for the development of DMt2. A higher BMI in patients with DMt2 diagnosed before the age of 40 years may be one of the reasons for the earlier manifestation of diabetes in these people. On the other hand, in group C, a lower BMI can be considered as a factor protecting patients with a predisposition to developing DMt2 against earlier onset of the disease. The study did not show a relationship between the studied polymorphism and the occurrence of overweight and/or obesity in all the examined groups. The results of other studies evaluating the effect of the rs7903146 polymorphism of the *TCF7L2* gene on body weight are inconclusive [29, 30].

The presented study is an attempt to better understanding the role of *TCF7L2* polymorphism in pathogenesis of DMt2. There is no evidence that *TCF7L2* polymorphisms can serve as predictors of progression disease or influence response to pharmacotherapy. In spite of the ambiguous impact of this polymorphism on a number of clinical aspects of DMt2 patients, TCF7L2 seems to be one of the most important genetic factor in pathogenesis of DMt2. The impact of the polymorphism of *TCF7L2* may be affected by the origin of the study population. The major limitation of this study is the number of subjects enrolled. Because of low frequency of particular polymorphisms, studies comprising more patients are awaited.

Conclusions

The presented study showed that the proportion of patients with the TT genotype of the rs7903146 polymorphism of the *TCF7L2* gene is significantly higher among patients with DMt2 diagnosed before the age of 60 years than among those diagnosed at a later age. However, the relationship between the studied polymorphism and the BMI of the studied patients, the occurrence of overweight, obesity, coexistence of arterial hypertension, and the time from the diagnosis to implementation of insulin therapy has not been demonstrated. Nevertheless, the results should be treated with caution due to the relatively small number of patients. Further studies, both experimental and clinical, are necessary to determine the specific function of the *TCF7L2* gene in the regulation of carbohydrate metabolism, which may contribute to earlier identification of people who are at increased risk of developing DMt2 and improved treatment effects through appropriate therapy.

Conflict of interest

The authors declare to have no conflict of interest.

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