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ORIGINAL ARTICLE

Association of the rs7903146 variant (IVS3C>T) of TCF7L2 with the prevalence of the metabolic syndrome and its components in population from Ahvaz cohort study: a case-control study in Iran

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Abstract

Background The metabolic syndrome consists of a combination of metabolic abnormalities and genetic predisposition that both contribute significantly to its development. Numerous studies have established a strong association between single nucleotide polymorphisms (SNPs) of the rs7903146 variant in the TCF7L2 gene and the metabolic syndrome (MetS) as well as type 2 diabetes.

Objective The aim of this study was to assess the impact of rs7903146 on MetS and its components.

Methods For this cross-sectional study, 325 individuals aged 25 to 86 who were selected from the baseline data of the Ahvaz cohort study were examined. Body mass index, blood pressure, fasting blood glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured following standard protocols. MetS subjects were identified based on the National Cholesterol Education Program guidelines. Genotyping was conducted using the PCR-RFLP method.

Results Our findings revealed that individuals with the CT genotype of rs7903146 had an increased risk of MetS (OR 2.24; 95% CI, 1.26–3.98; $p < 0.006$). This genotype was also found to be associated with a higher risk of hypertension and low HDL cholesterol ($p < 0.05$). Moreover, plasma triglyceride levels were slightly higher in individuals with TT and CT genotypes, although not significantly so ($p = 0.06$).

Conclusion In conclusion, the CT genotype of the TCF7L2 rs7903146 polymorphism exhibited higher odds for MetS. While lifestyle factors and other genes are also implicated in MetS, our findings suggest that studying TCF7L2 polymorphisms in high-risk groups could contribute to the development of genotype-specific prevention or treatment strategies. However, further research is required to validate these results.

Keywords Metabolic syndrome · TCF7L2 · rs7903146 · RFLP

Introduction

Metabolic syndrome (MetS) is characterized by a combination of metabolic risk factors, including hypertriglyceridemia, low HDL cholesterol, abdominal obesity or high BMI, glucose intolerance or insulin resistance, hypertension, and microalbuminuria that increases susceptibility to diabetes and cardiovascular diseases [1].

Global statistics indicate that the prevalence of MetS is on the rise in European and Asian countries. In Iran, studies have estimated the prevalence of MetS to be between 21.9 and 31.1% [2].

While the exact pathogenesis of MetS remains unknown, it is important to acknowledge that it predominantly affects

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populations with high calorie intake and limited physical activity. Additionally, genetic predisposition plays a significant role in its development [3]. However, many of the genes involved in MetS are not yet well understood.

The TCF7L2 gene, located on chromosome 10q25.3, encodes a protein that plays an essential role in the Wnt signaling pathway. This pathway regulates adipocyte differentiation, adipokine secretion profiles, adipogenesis, and β-cell function [4, 5]. Disruption of this pathway can contribute to adipocytokine dysfunction and insulin resistance, both of which are risk factors for MetS [6, 7]. Abnormalities in the Wnt pathway, therefore, can lead to metabolic disorders [8]. Single nucleotide polymorphisms (SNPs) in the TCF7L2 gene can disrupt the Wnt signaling pathway [9].

Numerous studies have found an association between the rs7903146 SNP in TCF7L2 and MetS, as well as an increased risk of type 2 diabetes due to reduced insulin secretion [9–11]. However, some studies have reported no association between the rs7903146 variant and insulin resistance or MetS [12]. It is important to note that conflicting results across different populations may be attributed to variations in sample sizes or specific ethnicities.

Early identification, educational programs, and appropriate treatment can be effective in managing the complications of MetS [13], Therefore, it is crucial to conduct indigenous research to determine whether the TCF7L2 rs7903146 polymorphism predisposes individuals to MetS. In this study, we investigated the associations between the TCF7L2 SNP (rs7903146) and the prevalence of MetS and its components in individuals participating in the Ahvaz cohort study. Findings from this study can inform effective health programs in the future.

Materials and methods

Study design and participants

The data and sub-samples for this research were obtained from a 5-year follow-up cohort of the adult population (aged 25 to 86 years) in Ahvaz. The study population consisted of 142 men and 183 women. The diagnosis of metabolic syndrome was based on the Adult Treatment Panel III (ATP III) criteria, requiring at least three of the following five components: abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women), TG ≥ 150 mg/dl or use of medications to manage triglycerides, HDL ≤ 40 mg/dl in men and ≤ 50 mg/dl in women, systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or use of antihypertensive medication, and FBS ≥ 100 mg/dl or use of blood sugar-lowering drugs [7, 14].

Clinical analysis

Anthropometric and biochemical data were obtained from the 5-year follow-up cohort of the adult population in Ahvaz. The measurement of anthropometric and biochemical parameters was previously presented by Shahbazian et al. [15] in 2013.

DNA isolation and genotyping

The rs7903146 variant was genotyped using the PCR-RFLP method. Genomic DNA was purified from leukocytes in EDTA blood samples using the QIAamp DNA Mini Kit (Qiagen, Germany) following the manufacturer's instructions. The integrity and purity of the extracted DNA were evaluated using 1% agarose gel electrophoresis and NanoDrop (Thermo Scientific, USA) at wavelengths of 260 and 280 nm, respectively. The PCR reaction was performed as follows: step one, 5 min at 95 °C for enzyme activation; step two, 35 cycles of denaturation at 95 °C for 45 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s; and a final extension at 72 °C for 5 min. The sequences of the primers used for PCR are provided in Table 1.

The rs7903146 variant was genotyped using the PCR-RFLP method. The PCR-amplified product resulted in a 188-bp fragment. Subsequent digestion of the PCR product with the RsaI enzyme generated specific fragments based on the genotypes. Specifically, the presence of the TT genotype produced a 188-bp fragment, the CC genotype produced 159-bp and 29-bp fragments, and the CT heterozygous genotype produced all three fragments (188-bp, 159-bp, and 29-bp). The digestion products were separated by electrophoresis on a 2.5% agarose gel and visualized using a safe stain (Yektatajhiz Inc., Iran) under a UV transilluminator (Quantum ST4, France).

Statistical analysis

Statistical analysis was conducted using SPSS version 23.0 (IBM Corporation). The Hardy-Weinberg equilibrium was assessed using a simple chi-square test. Anthropometric and biochemical characteristics among genotypic groups were compared using chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Multivariable binary logistic regression, adjusted for age and gender, was performed to determine the independent association of different genotypes and alleles of rs7903146 with the prevalence of MetS. The associations were presented as odds ratios (ORs) with corresponding 95% confidence intervals

Table 1 The sequences of the primers used in the study

Forward sequences: 5′-ACAATTAGAGAGCTAAGCACTTTTTAG GTA-3′
Reverse sequences: 5′-GTGAAGTGCCCA AGCTTCTC-3′

(CIs). A significance level of $p < 0.05$ was considered statistically significant. The comparison was made between the CC genotype (as the dominant model) and carriers of the minor alleles (CT and TT) in the analysis.

Results

Characteristics of the study participants based on TCF7L2 rs7903146 genotype

The anthropometric and clinical characteristics of the study participants were analyzed based on their TCF7L2 rs7903146 genotype at the beginning of the study. The distribution of genotypes was found to be in accordance with Hardy-Weinberg equilibrium ($p > 0.05$). Although there was a tendency for carriers of the TT genotype to experience a decrease in plasma TG levels, the results did not reach statistical significance ($p = 0.06$). Furthermore, there were no significant differences observed in other variables based on genotype (refer to Table 2).

Association between TCF7L2 rs7903146 and MetS

Logistic regression analysis revealed that individuals with the CT genotype had a significantly higher prevalence of metabolic syndrome (MetS) compared to those with the CC genotype ($p = 0.004$; OR, 2.34; CI, 0.31–1.80). The dominant genetic model test indicated that carriers of the T allele (CT+TT) had a significantly higher prevalence of MetS compared to non-carriers ($p = 0.01$; OR, 2.06; CI, 1.18–3.60) (refer to Table 3).

Association between TCF7L2 rs7903146 and MetS components

Individuals with the CT genotype exhibited a significantly higher prevalence of hypertension compared to those with the reference genotype (CC) ($p = 0.02$; OR, 2.06; CI, 1.11–3.82). Under a recessive model, T allele carriers (CT+TT) demonstrated a significant difference in the prevalence of hypertension compared to other genotypes ($p = 0.02$; OR, 2.07; CI, 1.12–3.83), while the TT genotype exhibited a protective effect against hypertension compared to the (CT+CC) genotype ($p = 0.04$; OR, 0.34; CI, 0.12–0.95). Furthermore, the prevalence of low HDL cholesterol was significantly higher in CT carriers compared to the reference genotype ($p = 0.02$; OR, 1.76; CI, 0.49–2.20). However, in the dominant model, individuals with the T allele (TT+CT) showed lower HDL cholesterol levels than those with the CC genotype, although this difference did not reach statistical significance ($p = 0.07$) (refer to Table 4).

Table 2 Clinical characteristics of the study participants according to TCF7L2 rs7903146 genotype

Clinical data	Mean[b]/percent data level by genotype			*p* value[a]
	TT	CT	CC	
Number of participants (%)	43.69%	42.77%	13.54%	
Age (years)	47.0 ± 13.4	46.0± 13.4	47.7 ± 13.3	0.71
Sex (Male/female)	57/85	65/74	20/24	0.51
BMI (kg/m^2)	27.5± 5.0	28.0 ± 7.3	27.7±4.3	0.87
Waist circumference(cm)	91.0 ± 12.0	91.0± 11.0	93.0±11.0	0.55
Systolic blood pressure (mmHg)	115.2±15.5	116.0±14.2	112.1±13.2	0.34
Diastolic blood pressure (mmHg)	69.7±16.16	71.4± 14.4	71.3±11.0	0.62
Fasting plasma glucose (mg/dL)	104.2 ± 39.3	108.0±41.5	118.±60.0	0.18
Triacylglycerol (mg/dL)	143.0± 79.0	152.7±90.0	119.0±66.1	0.06
HDL cholesterol (mg/dL)	47.4 ± 9.3	45.3± 10.0	48.0 ± 8.2	0.11
Smoking (%)	10.6%	8.7%	11.6%	0.80
Abdominal Obesity (%)	58.5%	54.0%	63.6%	0.49
Hypertriglyceridemia (%)	36.6%	36.7%	22.7%	0.19
Low HDL cholesterol (%)	44.4%	53.2%	38.6%	0.15
Hypertension (%)	25.4%	28.8%	20.5%	0.52
Hyperglycemia (%)	40.1%	36.0%	43.2%	0.62
Metabolic syndrome, NCEP-ATPIII	39.3%	48.6%	12.1%	0.33

[a]All *p* values are for univariate logistic regression model, and $p < 0.05$ indicates significant differences

[b]The comparison between groups was based on the means ± standard deviation

Table 3 Association between TCF7L2 rs7903146 polymorphism and MetS based on logistic regression analysis

Rs7903146	Crude model		Adjusted model[b]	
	OR (95%CI)	*p* value	OR (95% CI)	*p* value
CC	Reference	-----	Reference	-----
CT	2.24 (1.26–3.98)	0.006*	2.34 (0.31–1.80)	0.004*
TT	1.33 (0.56–3.13)	0.51	1.78 (0.78–4.10)	0.17
C	1.17 (0.53–2.57)	0.69	---	----
T	1.99 (1.15–3.46)	0.01*	2.061 (1.18–3.60)	0.01*
TT+CT vs. CC(D)	1.99 (1.15–3.46)	0.01*	2.061 (1.18–3.60)	0.01*
TT vs. CC+CT(R)	0.85 (0.39–1.87)	0.69	---	-----

D dominant, *R* recessive, *OR* odds ratios, *CI* confidence interval

[b]Adjusted model, adjusted for age and gender

*Significant *p* values

Discussion

The metabolic syndrome is a complex condition influenced by various factors, including disrupted adipocytokine secretion and insulin resistance, leading to a pro-inflammatory and pro-thrombotic state [6, 7]. While metabolic syndrome is characterized by a combination of metabolic abnormalities, the prevalence of these risk factors can vary among different ethnic groups [7]. Several genomic studies have focused on the genetic susceptibility to metabolic syndrome, revealing significant associations with specific single nucleotide polymorphisms (SNPs) in genes such as FTO, TCF7L2, APOA5, APOC3, and IL6 [16].

TCF7L2 is a transcription factor involved in the Wnt signaling pathway [9] and expressed in various human tissues [17]. The rs7903146 polymorphism in the TCF7L2 gene has been extensively studied and strongly associated with metabolic syndrome and type 2 diabetes [16].

In this Ahvaz cohort study, we also found that the T allele and particularly the CT genotype of rs7903146 were linked to an increased risk of developing metabolic syndrome. This finding is consistent with previous research showing that T allele carriers who consume high levels of polyunsaturated fatty acids (PUFA) are more susceptible to metabolic syndrome, diabetes, and cardiovascular diseases [18]. Meta-analysis studies have further supported the strong association between rs7903146 and type 2 diabetes mellitus (T2DM) in diverse populations of Caucasian, East Asian, South Asian, etc. [19]. Furthermore, a study conducted by Mustafa et al. on the Iraqi Kurdish population indicated that individuals carrying the T allele are more susceptible to type 2 diabetes mellitus (T2DM) [20]. This association has been further confirmed in other

Table 4 The association between *TCF7L2 rs7903146* polymorphism and MetS components

TCF7L2 rs7903146	Abdominal obesity (W.C ≥ 102 cm in men, ≥ 88 cm in women)		High triglycerides (TG ≥ 150 mg/dl)		Low HDL cholesterol (HDL ≤ 40 mg/dl in men, ≤ 50 mg/dl in women)		High blood pressure (systolic BP ≥ 130 mmHg and or diastolic BP ≥85mmHg)		Hyperglycemia (FBS ≥ 100 mg/dl)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
CC	Reference	----	Reference	----	Reference	---	Reference	-----	Reference	-----
CT	0.84 (0.51–1.39)	0.51*	1.96 (0.54–7.05)	0.86*	1.76 (0.49–2.20)	0.02*	2.06 (1.11–3.82)	0.02*	1.24 (0.64–2.39)	0.51*
TT	0.76 (0.39–1.59)	0.47*	2.07 (0.58–7.42)	0.30*	0.93 (0.90–3.92)	0.85*	0.70 (0.24–2.01)	0.51*	0.79 (0.28–2.27)	0.67*
TT+CT vs. CC	0.80 (0.50–1.28)	0.36	0.94 (0.48–1.83)	0.85	1.53 (0.96–2.42)	0.07*	2.07 (1.12–3.83)	0.02*	1.10 (0.59–2.05)	0.75
TT vs. CC+CT	0.82 (0.41–1.04)	0.57	0.48 (0.14–1.63)	0.24	0.69 (0.35–1.39)	0.31	0.34 (0.12–0.95)	0.04*	0.71 (0.26–1.90)	0.49

*Data are adjusted according to age and sex. Statistical significance was determined at $p < 0.05$; values that was statistically significant was underlined

studies conducted on the Iranian population [21] and the Southern Brazilian population [22].

In contrast, studies conducted by Zheng et al. did not find any association between variants of rs11196218 or rs7903146 in the TCF7L2 gene and type 2 diabetes (T2DM) or fasting levels of proinsulin/insulin ratios in the Chinese population. Interestingly, the rs11196218 variant was identified as the most high-risk locus in the Chinese population [23]. Similarly, Marzi et al. [24] and Saadi et al. [25] did not observe a significant association between TCF7L2 variants and insulin resistance or metabolic syndrome in the MONICA/KORA study and Emirati subjects, respectively. The contradictory results observed in complex diseases like metabolic syndrome can pose a significant challenge [26], and it is likely that these inconsistencies arise from differences in sample size, ethnic heterogeneity, variations in defining metabolic syndrome, and the inherent heterogeneity of the syndrome itself [27].

Our study also revealed a significant association between the CT genotype and high blood pressure as well as lower levels of plasma HDL cholesterol. This is in line with findings from other cohorts, which demonstrated that the TCF7L2 rs7903146 polymorphism and reduced insulin secretion after glucose consumption were associated with increased incidence of hypertension [28]. However, our study found that the TT genotype was more protective against hypertension, contradicting this finding.

We did not observe an association between the TT genotype and metabolic syndrome components such as high triglycerides, low HDL cholesterol, hyperglycemia, hypertension, and abdominal obesity [29]. In contrast, Perez-Martinez et al., studying the effects of rs7903146 on postprandial lipid metabolism in elderly subjects (≥ 65 years), have shown that minor allele carriers have higher fasting plasma TG levels. Factors such as age and adiponectin levels may contribute to the variation in lipid profiles among TCF7L2 T allele carriers [30].

On the other hand, it was suggested that the decrease in triglyceride levels may be due to the inhibition of adipose tissue lipolysis and adipogenesis by the TCF7L2 minor variant [28]. A large body of evidence suggests that the Wnt/TCF7L2 signaling pathway is critical for adipocyte differentiation and the regulation of adipogenesis [9, 28]. The mentioned study also showed that among healthy young males, subjects with homozygous alleles have shown a worse postprandial lipid profile (a trend towards higher plasma triglycerides).

Based on the available evidence, it seems that the effect of the TCF7L2 rs7903146 polymorphism on MetS components is different and related to many conditions so that the T allele has a protective role in some of them and an enhancing role in others. Therefore, it complicates the interpretation of the results and makes other factors more prominent in the development of the metabolic syndrome.

It is important to consider that metabolic syndrome is a multifactorial condition influenced by various risk factors, and our study solely focused on the role of the TCF7L2 rs7903146 polymorphism. Further research should examine the involvement of other related genes and consider lifestyle factors, diet, and nutrition in the study population.

Conclusions

In conclusion, our study supports the association between the CT genotype of the TCF7L2 rs7903146 polymorphism and increased risk of hypertension and low HDL cholesterol, as well as higher odds of developing metabolic syndrome. Although TCF7L2 polymorphisms in high-risk populations could potentially inform genotype-specific prevention and treatment strategies, further research is warranted to validate these findings.

Author contribution NM conceived and supervised the study; MR and HS performed experiments; MTB and BC analyzed data; ND and MR wrote the paper. All authors read and approved the final manuscript.

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Data Availability Data will be made available on request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical clearance, consent of participant The study protocol was approved by the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (HLRC-9505), and informed consent was obtained from all participants.

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