ORGINAL ARTICLE

Association Between 3'APOB-VNTR Polymorphism and Plasma Lipid Profiles in Type 2 Diabetes Patients

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Abstract

Objective: Apolipoprotein B (APOB) plays an important role in the metabolism of cholesterol and impairment in its function can lead to cholesterol accumulation in the pancreatic islets. It can then reduce insulin secretion and lead to Type 2 diabetes (T2DM). The purpose of this study was to investigate the association of 3'APOB-VNTR polymorphism with plasma lipid profiles in T2DM individuals in Khorasan Razavi province, Iran.

Materials and Methods: In this case-control study, 204 patients with T2DM and 207 non-diabetic volunteers were examined as a control group. All samples were analyzed for plasma lipid profiles. Genotypes were determined by PCR and electrophoresis. Differences in lipid variables between genotypes were assessed using one-way analysis of variance (ANOVA) with SPSS 20.0.

Results: We found 18 different alleles of the APOB gene 3'VNTR comprising from 26 to 45 hypervariable elements (HVEs) in the control groups and 21 alleles ranging from 30 to 51 repeats in the T2DM patients. Short alleles (26 to 29 HVEs) were only in controls and large alleles (46 to 51 HVEs) were only in T2DM patients. Our results showed that in people with long HVE polymorphism, HDL-C levels decreased, but LDL-C increased. Therefore, longer alleles for T2DM are considered risk factors. It was also observed that the TC / HDL-C ratio was significantly lower in shorter genotypes than the longer genotypes in T2DM patients.

Conclusion: It is concluded that 3'APOB-VNTR polymorphisms, especially longer alleles, affect plasma lipid levels in individuals with T2DM and are risk factors for this disease.

Keywords: 3'APOB-VNTR, Polymorphism, Plasma lipid, Type 2 diabetes mellitus

Introduction

Type 2 diabetes (T2DM) is the most prevalent type of diabetes worldwide (90% of diabetic patients). T2DM is caused by complex interactions between environmental factors and certain genetic factors. An effective genetic factor is gene

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polymorphism, such as Apolipoprotein B (APOB) gene, which contributes to the metabolism of lipids. The factors involved in T2DM include many metabolic changes such as obesity, serum lipid profile, and hypertension. Some experimental studies have shown that cholesterol accumulation in the islands of Langerhans reduces glucose-stimulated insulin secretion (GSIS) and reduces glucose tolerance in mice. Therefore, high cholesterol levels may be a risk factor for glucose intolerance and diabetes (1).

APOB is a component of serum lipoprotein types such as chylomicron, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), and also a ligand for LDL receptor (2). Apo B plays a major role in the metabolism of cholesterol, and it is suggested that APOB gene polymorphisms may alter serum lipids and glucose levels in patients with T2DM (3-5). Therefore, it is important to study the relationship between the Type of APOB gene with the lipid profiles and T2DM in each ethnic group. Although some studies have investigated its association with plasma lipid levels, not in diabetics (6,7). Several polymorphisms have been identified in the APOB gene. A specific polymorphism called variable number of tandem repeats (VNTR) is located 75 bp downstream of the second polyadenylation signal at the end of 3 APOB genes (2p24-p23) and is common in some ethnic groups. (8,9).

3'APOB-VNTR polymorphism has been reported to be associated with changes in serum lipid concentrations (10-16). Therefore, the aim of our study was to investigate the association of 3'APOB-VNTR polymorphism with plasma lipid profiles in an Iranian population with type 2 diabetes and to compare it with non-diabetic individuals.

Materials and Methods

Subjects and samples

In this case-control study, blood samples (5 ml of each subject) from 204 T2DM patients (male=39 and female =165) were collected in hospitals affiliated to Neyshabor University of Medical Sciences and Social Security Hospitals in Neyshabur, Shahr-e Firouzeh, Kashmar and Mashhad in Khorasan Razavi province. People who first referred to the hospital centers for diabetes tests and whose disease was confirmed by doctors were used as cases. The sample size was determined by Cochran's formula and sampling was done by simple random method. In addition, as a control group, blood was collected from 207 non-diabetic volunteers (male= 30 and female= 177) who matched the patient group in terms of age, sex, and residential area. People who were tested less than a month ago and found to be non-diabetic, as well as healthy people, were in the control group. These subjects voluntarily went to the biochemistry laboratory of the Islamic Azad University of Neyshabur or clinical centers for blood sampling. Not all individuals in the case and control groups had cardiovascular disease and no history of hyperlipidemia.

Clinical and biochemical measurements

For each participant, phenotypic variables including height, weight, waist and blood pressure were recorded. Blood samples were collected from subjects after 12 hours of fasting. The fasting blood sugar (FBS), total plasma cholesterol (TC), triglyceride (TG) and HDL cholesterol (HDL-C) levels were measured by an autoanalyzer (Suzuka Randox) using enzymatic colorimetric methods. The LDL cholesterol (LDL-C) was calculated using the Friedewald formula (17).

DNA extraction and determination of the 3'APOB-VNTR polymorphism

According to the purchased kit protocol (BioNEER, Cat. NO.: K-3032, Korea), genomic DNA was extracted from the peripheral blood of individuals.

Amplification of 3'APOB-VNTR was performed by polymerase chain reaction (PCR) using forward (5''-ATGGAAACGGAG AAATTATG-3'') and reverse (5''-CCTTCT CACTTGGCAAATAC-3'') primers (18-20). Reactions were carried out at a total volume of

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50 µl with 100 ng of genomic DNA; 20 pmol from each primer; 5 µLof 10 × buffer solution; 4 µL dNTP; and 2 U Taq polymerase. The amplification program consisted of initial denaturation at 94 °C for 5 minutes, 30 denaturation cycles at 94 °C for 40 s, annealing at 80 °C for 80 s, and extension at 72 °C for 1 min. The final extension was at 72 °C for 10 minutes. To detect 3'APOB-VNTR alleles, 6% agarose gel electrophoresis was performed at 80 mA for 2 hours.

The equation: repeat number = (fragment length (bp) – 138bp)/ 15 bp was used to calculate the number of tandem repeats. In this study, we used the nomenclature proposed by Ludwig et al. (19) and a short DNA sequence at the 3'-boundary of the hypervariable region was considered as a repeat (21).

The molecular size of each band was measured using gel quant software. The unknown samples were compared with DNA ladder 100bp purchased from Bioscience Company.

Statistical analysis

Kolmogorov‑Simonov goodness of fit test was used to assess the normality of the quantitative variable. Comparison of continuous variables was performed using independent T-test and presented as mean ± SD. Genotypes and phenotypes distribution between cases and controls were compared by the chi-square tests. Allele frequency was estimated by gene counting method. Hardy-Weinberg equilibrium tests were performed using genotype frequency and chi-square test with one degree of freedom.

SPSS 20.0 (SPSS Inc., Chicago, Illinois) statistical software package was used for statistical analysis. Statistical significance was assessed by two-sided tests. All *P*-values< 0.05 considered significant.

Ethical considerations

The protocol of the research was approved by the Medical Ethics Committee of Islamic Azad University (No: IR.IAU.NEYSHABUR.REC. 1395.8). Conscious consent was obtained from the participants.

Results

General and clinical characteristics

The general and clinical characteristics of T2DM patients and controls have been presented in table 1. Because the *P*-value was 0.000 for comparing waist, BP and FBS, these were significantly different. Also, because the difference between the mean HDL-C values between the two groups is 4.715 mg/dl and the *P*-value is 0.004, and the difference between the mean LDL-C values is 22.771 mg/dl and the *P*-value is 0.014, their difference is significant. However, due to the fact that *P*-values for BMI, TC and TG parameters are more than 0.05, there was no significant difference between the case and control groups.

Allelic frequencies and distribution of genotypes

According to the number of repeats of 15-bp hypervariable elements (HVE), 22 different alleles of the Apo B gene 3'VNTR comprising from26 to 51 HVEs were identified in T2DM and controls group (Figure 1). They were 26, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44 and 45 repeats in controls, and 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50 and 51 repeats in T2DM patients. HVE26-27-28-29 and HVE44 did not detect in T2D mpatients and HVE27-28 and HVE46-51 were not found in controls. Hence, larger alleles are only found in T2DM patients and shorter alleles are mainly detected in controls. The most frequent allele was HVE38 (29.4%), followed by HVE36 (14.7%) and HVE40 (13.2%) in T2DM, whereas the most frequent allele was HVE40 (21.7%), followed by HVE36 (20.2%) and HVE38 (17.3%) in controls. Totally, the most frequent allele in the two groups was HVE38 (23.3%), followed by HVE36 (17.5%) and HVE40 (17.5%).

For convenient analysis, the alleles were divided into a three-allele model. Up to 32 replicates in the short allele group (S), the most abundant alleles (33-31 replicates) in the

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medium (M) group and the long allele group (L) were more than 41 replicates. The frequency of 3'apoB-VNTR genotypes and alleles in healthy and T2DM groups is presented in table 2. There was no significant difference in genotype distribution and frequency of alleles between T2DM and control group (chi-square= 2.566, *P*-value= 0.855).

Influence of 3'APOB-VNTR polymorphism on general and biochemical profiles

General and biochemical profiles according to the genetic polymorphisms of 3'APOB-VNTR are shown in table 3. To investigate the relationship of individuals profile with the genotypes of the 3'APOB-VNTR, we divided subjects into six carrier subgroups: SS, SM, SL, MM, ML and LL. In T2DM, significant variation among the six genotypes was seen for HDLC, as well as among S (SS, SM, SL) and L (LL, ML, MM) alleles (*P*-value< 0.05). In controls, 3'APOB-VNTR polymorphism was significantly effective on plasma TG concentration (*P*-value< 0.05)**.**

Discussion

Before any discussion in the case of influence of the 3'APOB-VNTR on T2DM, should be mentioned, as shown in table 1, the results of our study like other studies demonstrated that there is a significant difference in the waist,

Table 1.General and Clinical profiles of the study population

Profiles		T2DM (n=204)	Controls (n=207)	*P*-value
Sex	**Male**	39 (19.1%)	30 (14.5%)	0.412
	Female	165 (80.9%)	177 (85.5%)	
Age (years)		54.6 (±11.0)	39.2 (±16.1)	0.0001*
BMI		27.8 (±3.8)	25.3 (±4.4)	0.004*
WC		99.4 (±12.3)	95.0 (±13.7)	0.0001*
SBP		134.3 (±2.3)	116.4 (±2.1)	0.0001*
FBS		174.0 (±85.1)	82.1 (±12.3)	0.0001*
TG		157.4 (±101.8)	134.7 (±58.6)	0.078
TC		207.6 (±46.5)	198.4 (±48.9)	0.176
LDL-C		140.9 (±23.2)	118.1 (±12.3)	0.014*
HDL-C		41.3 (±9.7)	46.0 (±38.1)	0.004*

BMI, body mass index (Kg/m^2); WC, waist circumference (cm); SBP, systolic blood pressure (mmHg); FBS, fasting blood sugar (mg/dl); TC, total cholesterol (mg/dl); TG, triglycerides (mg/dl); HDL-C, high-density lipoprotein cholesterol (mg/dl); LDL-C, low-density lipoprotein cholesterol (mg/dl). The difference between the sexes in the two groups was compared using chi-square and their number (%) was given, but the rest were compared using t-test and presented as mean (±standard deviation). * *P*-value < 0.05. .

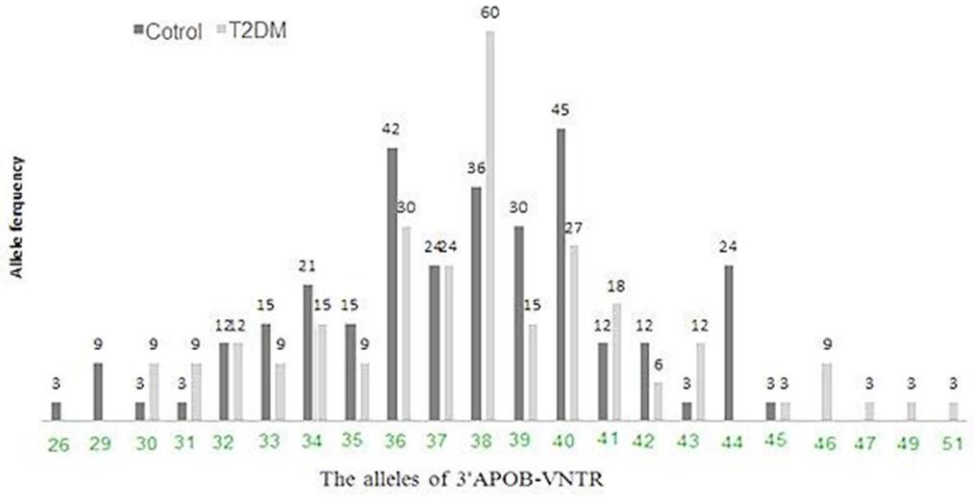

Figure 1. The frequency distribution of the 3'APOB-VNTR alleles between controls and T2DM patients; *P*-value < 0.01 (HVE36, HVE38 and HVE40), in comparison between T2DM and Controls.

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BMI, BP, FBS, HDL-C and LDL-C, but no significant difference in the TC and TG between T2DM patients and controls. What is more important is that waist size was also directly related to T2DM, which means that people with high waists are more likely to develop diabetes, so everyone should be careful not to increase their waist size. These findings are in agreement with those of other studies (18). Also, in the present study, because LDL-C concentration was significantly more and HDL-C concentration was less in T2DM than controls and as mentioned in the introduction the accumulation of cholesterol in the islets of Langerhans is associated with a decrease in the secretion of glucose-stimulated insulin (GSIS) and thus causes glucose intolerance in rats (1). Therefore, increasing cholesterol levels can be a risk factor for glucose intolerance and the incidence of diabetes.

Hyperlipidemia is a complex condition caused by a variety of environmental and genetic factors. About half of the differences in LDL-C concentrations are due to genetic factors (19). Several studies have shown that that 3'APOB-VNTR polymorphism is associated with changes in plasma lipid concentrations

Table 2. Distribution of 3'APOB-VNTR genotypes and alleles

Genotype or Allele	T2DM N (%)	Controls N (%)	*P*-value
SS	18 (8.8)	15 (7.2)	
SM	6 (2.9)	6 (2.9)	
SL	3 (1.4)	0 (0.0)	
MM	120 (58.8)	141 (68.1)	0.865
ML	36 (17.6)	24 (11.6)	
LL	21 (10.3)	21 (10.1)	
S	27 (13.2)	15 (7.2)	0.0001
M	162 (79.4)	180 (87.0)	0.0001
L	60 (29.4)	48 (23.2)	0.0001

Genotypes and Alleles distribution between T2DM and controls were compared by the chi-square tests.

Table 3. Influence of 3'APOB-VNTR polymorphism on general and biochemical profiles in T2DM and control subjects.

Subjects / Profiles	Genotypes						*P*-value
T2DM	**SS**	**SM**	**SL**	**MM**	**ML**	**LL**	
Age (years)	49.8 (±8.1)	62.0 (±11.2)	56.0 (±12.2)	55.4 (±8.7)	56.3 (±8.9)	49.0 (±11.9)	0.547
BMI	27.8 (±4.5)	26.8 (±4.7)	25.9 (±4.2)	27.6 (±5.1)	27.8 (±4.1)	31.5 (±5.5)	0.663
SBP	13.7 (±1.9)	13.7 (±2.1)	13.4 (±2.0)	13.4 (±2.4)	12.8 (±2.3)	14.0 (±2.5)	0.626
WC	92.0 (±13.9)	110.5 (±14.9)	99.4 (±12.5)	100.3 (±12.9)	97.2 (±13.0)	105.5 (±14.1)	0.385
FBS	176.4 (±86.1)	125.0 (±81.7)	128.0 (±82.8)	164.9 (±85.0)	182.2 (±87.5)	175.4 (±85.1)	0.892
TG	163.2 (±100.9)	170.0 (±101.8)	163.0 (±102.1)	155.6 (±102.0)	139.0 (±80.5)	122.8 (±103.1)	0.968
TC	172.8 (±45.5)	223.5 (±46.1)	225.5 (±44.5)	199.8 (±44.9)	192.7 (±43.4)	190.0 (±45.4)	0.791
LDL-C	93.0 (±23.4)	119.0 (±22.4)	130.2 (±23.6)	115.3 (±22.8)	108.1 (±24.4)	134.0 (±21.9)	0.349
HDL-C	57.8 (±10.7)	47.6 (±11.0)	43.1 (±9.9)	34.3 (±12.0)	38.9 (±9.7)	32.5 (±10.1)	0.006*
TC/HDL-C	2.991	4.704	5.230	5.817	4.951	5,846	0.045*
Controls	**SS**	**SM**	**SL**	**MM**	**ML**	**LL**	
Age (years)	45.6 (±8.6)	48.5 (±9.1)	-	37.0 (±13.9)	36.5 (±10.1)	48.7 (±11.8)	0.343
BMI	25.6 (±4.8)	25.6 (±4.5)	-	24.9 (±5.1)	26.4 (±4.7)	27.2 (±4.4)	0.853
SBP	12.0 (±2.2)	14.5 (±2.3)	-	11.1 (±2.0)	12.3 (±2.5)	13.0 (±2.4)	0.142
WC	103.0 (±13.1)	88.5 (±13.5)	-	88.5 (±12.9)	99.0 (±12.8)	111.0 (±13.0)	0.667
FBS	91.2 (±8.1)	91.0 (±18.4)	-	80.4 (±11.1)	80.9 (±17.9)	85.7 (±12.5)	0.341
TG	126.7 (±58.1)	145.0 (±57.1)	-	114.0 (±55.9)	163.5 (±58.8)	199.8 (±54.3)	0.028*
TC	210.7 (±46.1)	210.0 (±46.5)	-	200.8 (±45.6)	211.8 (±45.9)	232.0 (±44.3)	0.819
LDL-C	109.3 (±13.4)	118.0 (±13.0)	-	113.5 (±12.4)	121.0 (±12.8)	132.0 (±11.8)	0.881
HDL-C	41.0 (±37.7)	37.5 (±31.0)	-	44.5 (±27.1)	46.2 (±20.3)	47.0 (±17.9)	0.793
TC/HDL-C	5.138	5.6000	-	4.507	4.578	4.936	0.650

BMI, body mass index (Kg/m^2); SBP, systolic blood pressure (mmHg); WC, waist circumference (cm); FBS; fasting blood sugar (mg/dl); TC, total cholesterol (mg/dl); TG, triglycerides (mg/dl); HDL-C, high-density lipoprotein cholesterol (mg/dl); LDL-C, low-density lipoprotein cholesterol (mg/dl); Mean (±standard deviation) is provided; * *P*-value < 0.05**.** One-way analysis of variance (ANOVA) was used to assess the differences of variables among the genotypes.

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(10-16). Therefore, we guessed that genetic factors will involve in the results of our study. According to our knowledge, this is the first study on the association of this polymorphism with T2DM in this ethnic group. Our findings showed HDL-C levels in T2DM patients is significantly related to 3'APOB-VNTR polymorphism, as with increase HVE the levels of HDL-C decrease, but in contrast with HDL-C, the LDL-C increase, as shown in table 3. Thus, HVE with a shorter length can be an advantage for T2DM. In our study, we observed that TC/HDL-C ratio was significantly lower in Short than in long genotypes of 3'APOB-VNTR polymorphism in T2DM patients, thus, this factor is also a determinant for T2DM.

Results of our present study showed that carriers MM genotype of 3'APOB-VNTR polymorphism, that they are in the majority, in the controls group have better profiles of FBS, TG, TC, LDL-C, Waist, BMI and BP than carriers SS and LL. Thus, HVE with larger or shorter length has a totally negative effect on clinical and biochemical parameters in the controls group, but not significantly. This state does not have regularity in T2DM. Also, it is to be mentioned that higher plasma TG levels in control subjects were significantly associated with an increase in numbers of HVE. Choong et al. (20) showed that TC, LDL-C and TG levels are high in people with L allele (> 41 repeat units) and HDL-C levels are low in Malay and Indian Singapore, whereas, in Chinese individuals, the L allele only caused a significant increase in TC and TG levels. In a study, Ho et al. (22) also showed that people with long allele (L) had lower total cholesterol and LDL-C cholesterol than medium (M) or short (S) alleles. A study in Italy also showed that there is a specific relationship between the 3'APOB-VNTR allele and the lipid parameters in the southern Italian population (12). In contrast, a Taiwanese study of CAD and controls concluded that the length of the 3'APOB-VNTR polymorphism was not associated with lipid profiles (23). Other studies also found that there was no significant association between the 3'VNTR alleles and serum lipid levels in the Finnish and Kuwaiti populations. (24,25).

In addition to the above discussion, the diversity between 3'APOB-VNTR among different populations is important and should be discussed. We know the VNTRs are multiallelic and don't vary from generation to next. Thus, these markers would be useful and informative to study genetic variation among the human population. Although genotypes of 3'APOB-VNTR polymorphism have been studied relatively widely in the world, but currently no information is available on Iranian ethnic groups, so this study is the first study among an Iranian population. In our study, we observed that 18 different alleles of the 3'APOB-VNTR comprising from 26 to 45 HVEs to be in healthy individuals. They were 26, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44 and 45 repeats. Although, there were 21 alleles ranging from 30 to 51 repeats in the T2DM patients and the alleles were 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50 and 51 repeats, but there is no significant difference between T2DM patients and controls (Figure 1 and Table 2). Different numbers of HVE have been detected in different populations. For example, a study in healthy individuals from the Russian Federation and the Republic of Belarus found 25 alleles of the 3'APOB-VNTR minisatellite, ranging from 25 to 55 replicates (26). Deka et al (27) in a study on the distribution of alleles in the Apo B gene in 5 human populations, they found 12 separate alleles in 319 individuals. So, in the French population 12 different alleles (21), 19 in the India (28), 24among Bangladesh were identified at the 3'APOB-VNTR loci. Alleles 37 and 39, which are the most common alleles, were present in all populations. Therefore, in general, very different alleles are seen in different populations.

Conclusions

Finally, considering our findings and some other studies, we can conclude that 3'APOB-

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VNTR polymorphism has an effect on plasma lipid levels and incidence of T2DM. So shorter HVE can be an advantage and a longer length is a disadvantage to increasing atherogenic lipids and thus for T2DM. However, this is a preliminary study and the results need to be confirmed on a larger scale and further studies in order to consider this polymorphism as a marker of lipid elevation and possibly diabetes.

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Conflict of Interest

The authors declared that they have no conflict of interests.

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