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Original article

Prevalence of ApoB100 rs693 gene polymorphism in metabolic syndrome among female students at King Abdulaziz University

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ABSTRACT

Apolipoprotein B100 (ApoB100) is a glycoprotein and a member of the adipokine family. It plays a central role in lipoprotein metabolism. Many research studies have revealed a strong relation between ApoB100 and metabolic syndrome (MetS) and insulin resistance.

In our research, we examined the relationship between ApoB100 rs693 gene polymorphism, body mass index (BMI) and the probability of MetS in young female students studying at King Abdulaziz University (KAU) in Saudi Arabia. The study group comprised 141 females whose ages ranged from 18 to 25 years. Anthropometric measurements and biochemical parameters were measured alongside a genetic analysis of ApoB100 rs693.

The BMI, glucose concentration and total cholesterol level were found to be significantly associated with the ApoB100 rs693 gene. The differences noted between control and MetS groups regarding glucose concentrations were statistically significant ($P = 0.001$).

A growing number of young females are being diagnosed with MetS in KAU because of unhealthy eating habits, in combination with the absence of physical exercise, causing increased body weight and the potential progression of chronic diseases. Our study showed that the allele associated with hypertensive individuals at ApoB100 rs693 and MetS may have a direct genetic influence. Further research on expanded sample sizes, however, is required in order to draw rigid conclusions.

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1. Introduction

Metabolic syndrome (MetS) is a non-communicable (aggregation) disease (NCD) that causes early morbidity and mortality (Terzic and Waldman, 2011). MetS is a mixture of health conditions that causes an elevation in the risk of coronary heart disease (CHD) and diabetes mellitus type 2 (DMT2) (Hunt et al., 2004). Symptoms include elevated triglycerides (TG) and apolipoprotein B (ApoB100) which contains lipoproteins, being low in high-density lipoprotein (HDL), having high blood pressure and being obese (Harper and Jacobson, 2010).

MetS has been increasing in the past few years especially in overweight and obese people. About 25% of the world's population was estimated to have MetS (O'Neill and O'Driscoll, 2015). This study will particularly determine the prevalence of MetS in female students at King Abdulaziz University.

ApoB100 is one of the apolipoproteins that plays an essential part in lipoprotein metabolism. It is present in the plasma in two forms: a short form called apolipoprotein B-48, and a longer form known as apolipoprotein B100. The previous are components of lipoproteins, which present as fat and fat-like particles such as cholesterol in the bloodstream (Das et al., 2009).

ApoB100-48 is formed in the intestine and it is the precursor of chylomicrons that carry fat and cholesterol from the intestine into the bloodstream after food is digested. Chylomicrons are also important for the absorption of fat-soluble vitamins (Welty et al., 1999). ApoB100 is produced in the liver and is the building block for very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs). These linked molecules carry both fats and cholesterol in the bloodstream (Devaraj and Jialal, 2019; Segrest et al., 2001).

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ApoB100 is a anchor for the receptor-mediated the elimination of low density lipoprotein LDL (LDL is one of a lipoproteins group, which causes mainly heart diseases (Ference et al., 2017)) particles from the circulation (Kowal et al., 1989). A positive relation between CHD and LDL cholesterol with ApoB100 levels has been reported (Brunzell et al., 1984).

The gene coded for human ApoB100 has been located on the short arm of chromosome 2p23-24 with an approximate length of 43 kilobases and 29 exons (Chan, 1992; Deeb et al., 1986). Substantial gene diversity involves two ApoB100 signal peptide alleles, is a 43 kb in length with 81 bp coding for 27 and 24 amino acid peptides (Visvikis et al., 1990).

Several Single nucleotide polymorphisms (SNPs), have been found in the ApoB100 gene. Although the role of most of them is still under investigation, it has been reported that rs693 is the most common SNP which affects susceptibility to MetS. In the literature it has been associated with lipemic levels (Alves et al., 2020), it increased the risk of breast cancer in a study done by Liu in 2013 (Liu et al., 2013) and with lipid traits and cardiovascular disease risk factors (Park et al., 2011).

In the current study, we first tested the correlation between the ApoB100 polymorphism rs693 and MetS phenotypes. BMI, blood pressure, insulin resistance and waist circumference (WC) were used as indicator of obesity. To validate the functional consequence of ApoB100 polymorphisms, we measured ApoB100 expression levels in human adipocytes.

2. Methodology

Written consent was collected from all participants as the objectives and methodology of the study were clarified to them. The respondents were asked to fill out a survey containing questions about their lifestyle, body mass index (BMI) and general health issues. The study was approved by the Biomedical Ethics Unit, Faculty of Medicine, KAU (Approval Number 172–18).

A value of BMI < 18.5 kg/m^2 was considered as underweight, 18.5–24.9 kg/m^2 was considered as normal weight, 25.0–29.9 kg/m^2 was considered as pre-obese (overweight), and a BMI of 30 and more was considered as obese (Al-Nozha et al., 2005). Hypertension was defined as systolic blood pressure (SBP) of ≥140 mm Hg, diastolicblood pressure (DBP) of ≥90 mm Hg (Joint National Committee on Prevention Evaluation, and Treatment of High Blood Pressure, 1997). The data collected from 141 students at KAU was analyzed into tables as needed. Blood samples of around 5 ml from each volunteer were collected in plain and ethylenedi-aminetetraacetic acid (EDTA) tubes. Normal routine tests were performed on the blood samples, such as white blood cells (WBS) glucose, total cholesterol (TC), HDL, TG, LDL and uric acid concentrations in serum using commercial kits (Human Gesellschaft für Biochemica und Diagnostica GmbH, Germany). Serum levels of insulin resistance kit were purchased from Elabscience Biotechnology Co. Ltd, Hubei, China.

Genomic DNA was isolated from whole blood collected in EDTA anticoagulated tubes using a commercial kit (QIAamp DNA Blood Mini Kit; Hilden, Germany), according to the manufacturer's instructions. All DNA sample concentrations were measured using the Thermo Scientific NanoDrop 2000 Spectrophotometer in order to determine the purity of the samples. The Spectrophotometer was adjusted by using nuclease-free water as a blank to which samples were added using the Micro-Volume Pedestal method. DNA samples were genotyped using the 2 × TaqMan Master Mix, (Applied Biosystem, cat no. 4304437). All PCR primers of the selected gene candidates and the fluorescent dual-labeled TaqMan Probes were manually designed using primer 3 software. The region of interest within the ApoB100 gene (rs693) [A/G] was

amplified by using Polymerase Chain Reaction (PCR) technique. The forward primer (5′- ACATTCGGTCTCGTGTATCTTCTAG-3′) and the reverse primer (5′- GTCTCTCGGAATTTGGCCTTCATGT-3′) sets were used.

2.1. Statistical analysis

Statistical analysis of the data was carried out using the Statistical Package for Social Science SPSS (version 23.0). Variables were expressed by mean ± standard deviation (SD). The significant difference between normal individuals and those with obesity was illustrated using an unpaired student "t" test for parametric parameters.

The result was considered statistically significant when $p < 0.05$. Genotype deviation from the Hardy–Weinberg equilibrium was assessed using a chi squared test with one degree of freedom.

Genotype distributions are shown as a percentage value (%). The proportions of genotypes and alleles were compared by X^2 analysis, with a p-value according to chi-square tests, Odds ratios (OR) and a 95% confidence interval (CI), X^2 (degrees of freedom, N = sample size) = chi-square statistic value, p = p-value. The analyses were done first per genotype and then per allele.

3. Results

3.1. Characteristics of the population studied

The clinical characteristics of the MetS and the control groups are shown in Table 1. The mean BMI (kg/m^2) of these groups was 30.3 ± 8.2 and 22.1 ± 4.6, respectively. When comparing MetS subjects to controls, the findings showed a highly significant difference

Table 1
Characteristics of the population studied.

Characteristics	All BMI Categories (n = 141)		p
	Control n = 111	MetS = 30	
BMI (kg/m^2)	11	30	< 0.001 *
	22.1 ± 4.6	30.3 ± 8.2	
WC (cm)	110	30	< 0.001*
	71.6 ± 12.2	92.1 ± 12.7	
SBP (mmHg)	109	29	0.699
	106.3 ± 12.9	107.3 ± 11.7	
DBP (mmHg)	109	29	0.309
	71.0 ± 9.0	74.0 ± 10.0	
FBS (mg/dl)	104	30	< 0.001*
	94.4 ± 21.5	113.9 ± 31.0	
TC (mg/dl)	68	28	0.158
	207.8 ± 85.7	229.5 ± 83.6	
HDL (mg/dl)	85	25	0.566
	74.4 ± 47.8	70.6 ± 49.8	
LDL (mg/dl)	64	28	0.179
	137.4 ± 86.0	157.6 ± 72.6	
TG (mg/dl)	68	28	< 0.001*
	155.3 ± 90.3	215.7 ± 82.3	
Uric Acid (mg/dl)	68	28	0.010
	6.4 ± 2.8	8.4 ± 3.5	
WBC (X 10^3/uL)	83	29	0.006*
	6.2 ± 1.7	7.3 ± 1.8	
Insulin (µl/mL)	95	27	0.096
	3 ± 9	1 ± 0.5	
IR %	95	27	0.319
	13 ± 44	6 ± 4	

Data were expressed as mean +/- standard error of mean, BMI: Body mass index, WC: Waist Circumferences, SBP: Systolic blood pressure, DPB: Diastolic blood pressure, FBS: Fasting blood glucose, FB: Fasting blood glucose, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides, WBC: White Blood Cells, IR: Insulin resistance. A p-value < 0.05 was considered statistically significant.
*Significant.

between these groups regarding measurements of BMI ($p < 0.001$), WC ($p < 0.001$), fasting blood sugar (FBS) ($p < 0.001$), Serum triglycerides TG ($p < 0.001$), and WBS ($p < 0.006$). No significant difference between MetS and the control group with respect to SBP and DBP.

According to the participants' (n = 141 female students) BMI measurements as shown in Table 2, 47% (n = 66 students) were of normal weight, the majority of whom made up 56% of the control group (n = 62). While 21% (n = 29 students) were underweight, and all of them were recorded within the control group constituting 26% of the total participants (n = 29). On the other hand, 1% (n = 25 students) were overweight, and 15% (n = 21 students) were obese. Consequently, most of the subjects were within the standard range of the BMI. The majority of the MetS group was noted to be on the overweight scale or obesity scale with 47% (n = 14 students) and 40.7% (n = 12 students) respectively.

3.2. Genotype analysis

The genetic information obtained from study samples from, n = 141 (30 MetS and 111 control), female students was used in this analysis. All genotype distributions for the variables tested were in Hardy-Weinberg equilibrium (Edwards, 2008).

3.2.1. Comparison of the genotypic distribution (AA/AG) of ApoB100 rs693AG SNPs between MetS and control subjects

A chi-square test of independence was performed to examine the relation between MetS and control subjects. The relation between these variables was not significant, X^2 (1, N = 109) = 1.54, $p = 0.283$, demonstrating no significant difference between MetS and the control group with respect to the AA/AG genotype (Table 3).

3.2.2. Comparison of the genotypic distribution (AA/GG) of ApoB100 rs693AG SNPs between MetS and control subjects

A chi-square test of independence was performed to examine the relationship between MetS and control subjects. The relation between these variables was not significant, X^2 (1, N = 111) = 1.359, $p = 0.244$, demonstrating no significant difference between MetS and the control group in respect to the AA/GG genotype (Table 3).

3.2.3. Comparison of allele distribution (A/G) of ApoB100 rs693AG SNPs between MetS and control subjects

A chi-square test of independence was performed to examine the relation between MetS and control subjects. The relation between these variables was not significant, X^2 (1, N = 200) = 0.362, $p = 0.547$, demonstrating no significant difference between MetS and the control group with respect to the A/G allele (Table 3).

3.2.4. Risk factor and odd ratio associations with MetS in ApoB100 rs693AG SNPs

Odd ratio (OR) and risk estimates for MetS in the ApoB100 polymorphisms were presented in Table 4. The OR and risk associated with MetS in AA and AG genotypes were roughly equal to that associated with the AA/GG genotype. The relative risk for AA/AG and AA/GG were 1.267 and 1.296 respectively. Of this SNP, AA/AG genotype had a risk of MetS (OR 0.588, 95% CI (0.222–1559))

and AA/GG genotype had (OR 0.563, 95% CI (0.213–1.490)). The relative risk for A/G were 1.093 and the OR and risk associated with MetS in A/G allele were: (OR 0.834, 95% CI (0.821–1.456)).

3.2.5. The association of ApoB100 rs693 AG SNPs with the clinical characteristics of the study population

Table 5 presents the association of APOB100 rs693AG SNPs with the clinical characteristics of the study population. In control and MetS subjects, BMI, glucose concentration and TC concentration were significantly associated with the ApoB100 gene but none of the obesity related parameters (TC, TG and HDL) were associated with genotypes of ApoB100 (Table 5).

4. Discussion

Saudi Arabia is recognized as one of the world's top nations with regards to high rates of diabetes and obesity which have a major impact on most of the population in all age groups (Alqarni, 2016). MetS is a clustering of risk factors for DMT2, CHD, fatty liver and several cancers. Among the population, the prevalence of metabolic syndrome seems to be growing, notably in women of childbearing age (Ramos and Olden, 2008). Metabolic syndrome, associated with environmental factors, is strongly assumed to be due to genetic predisposing factors (Joy et al., 2008). ApoB100, synthesized by the liver, and mainly located on the surface of LDL, is a marker protein for atherosclerosis and other diseases and plays a key role in cholesterol homeostasis (Walldius et al., 2001).

Many candidate gene polymorphisms, such as estrogen receptor alpha, are associated with metabolic syndrome (Ghattas et al., 2013). They include tumor necrosis factor alpha (Gupta et al., 2012), angiotensin converting enzyme (Xi et al., 2012), increasing fat mass, obesity-associated protein and cholesteryl ester transfer protein (Povel et al., 2011). ApoB100 is an indicator for atherogenic risk because it is found to be associated with low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non–HDL-C) (Wilkins et al., 2016). ApoB100 is present within each lipoprotein particle, also in VLDL, chylomicron and intermediate density lipoprotein, with about 90% of ApoB100 is found in LDL (Sniderman and Marcovina, 2006). A report confirmed a significant relationship between ApoB100 and MetS independent of the LDL-C level in patients with DMT2 (Lim et al., 2015).

A study conducted on a group of females in Saudi Arabia found that the prevalence of MetS increases with an elevated BMI (Balgoon et al., 2019). In comparing genotypic distribution (AA/AG) of ApoB100 rs693AG SNPs between MetS and control subjects the results showed no significant difference, X^2 (1, N = 109) = 1.54, $p = 0.283$, although the normal allele A had 35 carriers compared to the G allele with 65 carriers. In a recent publication, Wang et al. (2018) found that T allele (CT + TT) carriers associated with rs693 for the plasma TC, TG, HDL-C and LDL-C levels have greater levels of TC when compared to T allele non-carriers (Wang et al., 2018). Another Chinese study found that the polymorphisms of rs693 and rs1042031 in the *APOB100* gene increases the risk of breast cancer independently of the BMI (Liu et al., 2013).

Regardless of genotypes, our findings suggest that the rs693 of ApoB100 is significantly associated with higher levels of TG, TC, BMI and glucose in the MetS population as compared with the control group. These findings agree with a study reporting the association of rs693 polymorphisms found to be significantly linked to higher levels of ApoB100, TG, TC and LDL-C, and lower levels of HDL-C (Niu et al., 2017). Philips and his colleagues found that some ApoB100 polymorphisms other than ApoB100 rs693 may contribute to the risk of MetS (Phillips et al., 2011). Another research study showed a strong association between the rs1469513 variant

Table 2
Body Mass Index of female students of KAU participant in the study.

BMI categories (kg/m^2)	Control (n = 111)	MetS (n = 30)	Total (n = 141)
Underweight	29 (26%)	0	29 (21%)
Normal	62 (56%)	4 (13%)	66 (47%)
Overweight	11 (10%)	14 (47%)	25 (1%)
Students with obesity	9 (8%)	12 (40.7%)	21 (15%)

Table 3
Comparison of the genotypic distribution of ApoB100 rs693AG SNPs between MetS and control subjects.

Genotypes n (Freq%)]	Control n = 111	MetS = 30	Total n = 141	p
A/A	8 (38.1%)	13 (61.9%)	21 (100%)	0.3005
A/G	45 (51.1%)	43 (48.9%)	88 (100%)	0.8375
G/G	47 (52.2%)	43 (47.8%)	90 (100%)	0.678
Allele n (Freq%)	Control	MetS	Total	p
A	31 (47%)	35 (53%)	66 (65.2%)	0.629
G	69 (51.5%)	65 (48.5%)	134 (34.8%)	0.729

A p-value < 0.05 was considered statistically significant.

Table 4
The association between ApoB100 rs693AG SNPs and the risk of MetS.

		Relative risk for MetS	OR (95% CI)	95% Confidence Interval	
				Lower	Upper
Genotypes	**AA/AG**	1.267	0.588	0.222	1.559
	AA/GG	1.296	0.563	0.213	1.490
Allele	**A/G**	1.093	0.834	0.821	1.456

OR: Odd Ratio, CI: Confidence Interval.

Table 5
The association between ApoB100 rs693AG SNPs and the clinical characteristics of the study population.

Parameters	Gene	Control n = 111	MetS = 30	p value
BMI (kg/m^2)	AA	24 ± 5	36 ± 13	0.28
	AG	22 ± 5	31 ± 10	0.0001*
	GG	21 ± 4	30 ± 4	0.0001*
WC (cm)	AA	170 ± 91	253 ± 74	0.23
	AG	200 ± 81	210 ± 105	0.84
	GG	237 ± 82	248 ± 75	0.57
FBS (mg/dl)	AA	103 ± 27	125 ± 34	0.21
	AG	95 ± 23	114 ± 42	0.032*
	GG	97 ± 28	107 ± 20	0.63
TC (mg/dl)	AA	164 ± 79	267 ± 94	0.11
	AG	159 ± 117	229 ± 80	0.003*
	GG	157 ± 66	181 ± 54	0.32
HDL (mg/dl)	AA	202 ± 94	165 ± 27	0.53
	AG	126 ± 80	145 ± 76	0.57
	GG	149 ± 90	174 ± 87	0.52
LDL (mg/dl)	AA	2 ± 2	2 ± 1	0.67
	AG	1 ± 2	1 ± 2	0.40
	GG	2 ± 2	1 ± 1	0.16
TG (mg/dl)	AA	44 ± 29	45 ± 37	0.81
	AG	62 ± 54	59 ± 71	0.53
	GG	73 ± 197	146 ± 130	0.015
Insulin (µI/mL)	AA	1 ± 0.2	2 ± 1	0.80
	AG	3 ± 11	1 ± 0.3	0.21
	GG	3 ± 8	1 ± 0.2	0.35
IR (%)	AA	5 ± 1	10 ± 9	0.57
	AG	12 ± 38	6 ± 2	0.86
	GG	16 ± 52	5 ± 1	0.33

BMI: Body mass index, WC: Waist Circumferences, FBS: Fasting blood glucose, FB: Fasting blood glucose, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides, IR: Insulin resistance. A p-value < 0.05 was considered statistically significant.
*Significant.

of ApoB100, plasma lipid profiles, and phenotypes associated with obesity (Doo et al., 2015).

In conclusion, our findings revealed a significant association between polymorphisms of the ApoB100 gene (rs693) and the prevalence of metabolic syndrome and increased its risk with only its component traits i.e., higher levels of TG, TC, BMI and glucose in the study population. This finding supports the conclusion that in the investigated Saudi female population, ApoB100 gene (rs693) can still be a very informative marker as a Saudi-specific DNA fingerprinting as well as for evaluating the function of the ApoB100 gene in MetS components. However, a larger scale study is essential to confirm the viability of this marker in different ethnicities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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