ORIGINAL ARTICLE

Association of the IL6 Gene Polymorphism with Component Features of Metabolic Syndrome in Obese Subjects

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Abstract

Metabolic syndrome (MetS) is a risk factor for type 2 diabetes mellitus and cardiovascular disease. Obesity is a component of the metabolic syndrome. Several genetic variants are reported to be associated with obesity and hypo adiponectinemia, including ars1800796 polymorphism of the interleukin-6 (IL-6) gene. Since obesity is associated with inflammatory factors, the aim of this study was to investigate the association between this polymorphism and MetS and its related features. Obese patients with body mass index (BMI) ≥ 30 ($n = 182$) were recruited into this study and divided into two groups; 110 patients with MetS, based on the International Diabetes Federation (IDF) criteria, and 72 subjects without MetS. The anthropometric and biochemical data for the groups were compared. Genotyping was carried out using RT-PCR. The association of the genetic polymorphism with MetS and its components were assessed using univariate and multivariate analyzes. There was an association between the presence of the rs1800796polymorphism of the IL-6 gene, with BMI ($P = 0.031$), high-density lipoprotein (HDL) ($P = 0.010$) and low-density lipoprotein (LDL) ($P = 0.037$), while this genetic variant did not show any significant association with the presence of MetS as defined by the IDF. We demonstrate an association between the rs1800796 genetic variant of the IL-6 gene with components of MetS including BMI, and HDL-cholesterol, but not the MetS itself. Therefore, supporting further studies are warranted to investigate this point in a larger population.

Keywords Metabolic syndrome · BMI · Gene polymorphism · Obesity

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Published online: 15 April 2019

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Introduction

One of the critical conditions that have recently attracted the attention of healthcare organizations is metabolic syndrome. Metabolic syndrome (MetS) is defined by clustering of abnormal metabolic features that include high blood pressure, obesity, insulin resistance and pro-inflammatory state (Bagherniyae et al. 2017; Ahmadnezhad et al. 2018; Ghazizadeh et al. 2018). The risk of cardiovascular disease (CVD) associated with MetS is higher among women than men (Galassi et al. 2006). The prevalence of MetS is increasing globally, and this may be due in part to the rising prevalence of obesity (Ferrara et al. 2003; Lau and Muniandy 2013). Obesity is associated with the activation of inflammatory pathways and the production of abnormal cytokines (Mirhafez et al. 2015; Hasnain 2018). An increase in serum inflammatory cytokines (e.g., interleukin-6) level is observed in type 2 diabetes patients and may be involved in obesity and MetS (Hamid et al. 2005). Obesity is also a major cause of hypertension so that two-thirds of the prevalence of hypertension is directly related to obesity. Obesity is characterized by increasing adipose tissue mass. There is heterogeneity in the type of fat in different anatomical sites. Men and women with a normal body mass index (BMI) have the lowest mortality (Pérez et al. 2007). Obesity is also directly related to the risk of diabetes mellitus, hypertension and arterial diseases, insulin resistance and an increased risk of total mortality (Abate et al. 2016; Bhatheja et al. 2016; Gato et al. 2016; Sun et al. 2016). Approximately 67% of patients with diabetes type 2 have a BMI > 27 kg/ m^2 (Stephenson and Rose 2003). Obesity also has a negative impact on a variety of conditions, including complications of pregnancy, menstrual disorders, psychiatric disorders, urinary incontinence, metabolic disorders and increased risk of some types of cancer (Alexopoulos et al. 2016; Slattery et al. 2008). Several factors are related to the development of MetS and obesity. These include environmental factors (e.g., lifestyle, gender, and ethnicity) and genetic factors [e.g., single nucleotide polymorphisms (SNPs) including variants of the interleukin 6 (IL-6) genes. IL-6is a regulatory cytokine that is associated with the progression of cancer and some other illnesses such as hypertension and cardiovascular disease (Du et al. 2015; Rafiq et al. 2007; Timasheva et al. 2008; Ponnana et al. 2017). There is also an association between obesity with the rs1800796SNP, located in the promoter region of the IL-6 gene. The rs1800796 polymorphism may affect the transcriptional efficiency of the IL-6 gene (Wang et al. 2016). Previous studies have shown a relationship between the (G > C) IL-6 (rs1800796) and body size so that people with the G allele have a lower waist-to-hip ratio (Slattery et al. 2007). Given the importance and relevance of obesity with cytokines and inflammatory factors such as IL-6 (Park et al. 2005; Dandona et al. 2004), the purpose of this study was to assess the relationship between the rs1800796S-NPandthe presences of MetS in an obese group of Iranian individuals.

Material and Methods

Study Population

The 182 obese subjects (BMI ≥ 30) were selected at random from the Heart Atherosclerotic disorders and Mashhad stroke and (MASHAD:2010–2020). Informed written consent was obtained from all participants, and the research protocol was approved by the Ethics Committee of the Mashhad University of Medical Science. Exclusion criteria of subjects included any acute or chronic disease, pregnancy, and alcohol consumption, taking any medications. Inclusion criteria of patients included: age of 18, or above, and completion of the informed consent form. The inclusion criteria for the non-MetS group were a lack of any classical cardiovascular risk factors. The criteria used for defining MetS were based on the definition of IDF (International Federation of Diabetes): central obesity (waist circumference of ≥ 94 cm for male or ≥ 80 cm for female), and two of these include HDL < 40 mg/dl in males, < 50 mg/dl in females, TG: ≥ 150 mg/dl, systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg, fasting blood glucose ≥ 100 mg/dl (Sirdah et al. 2012).

Laboratory Evaluations

Anthropometric parameters including weight, height, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum C-reactive protein (CRP) in all the subjects were measured using standard procedures as described.

BMI was calculated by dividing the weight (kg) by height (m). SBP and DBP were measured with subjects in the sitting position using a standard mercury sphygmomanometer on the left arm after a 15-min rest using a standardized method and the mean of two readings recorded. A third measurement was taken, if the difference between two measurements was more than diastolic 15 mm Hg or systolic 25 mm Hg, and the average of the two closest readings was used as the mean blood pressure. After a 12-h overnight fast FBG, samples were collected to determine serum glucose, lipid profile level (TC, TG, and HDL-C), and hs-CRP using an auto-analyzer (Eppendorf, Germany). LDL-C was then determined using the Friedewald formula if serum TG level was < 400 mg/dl.

Blood samples were taken from an antecubital vein and collected into vacuum tubes (20 ml). The centrifugation was performed at room temperature for 20 min at $1500 \times g$ to separate the serum and sample, and samples were stored at −80° C until analysis (Sun et al. 2014; Matsui et al. 2015).

Genetic Evaluations

Leukocytes DNA was extracted from blood using commercial kits (Blood DNA Extraction Kit and QIAamp®DNA Mini-Kit (Qiagen, SanDiego, CA), and the quantity and quality of the extracted DNA was assessed using a NanodropEpoch (Nano Drop-Technologies, Wilmington, USA). Genetic analysis for the rs1800796polymorphism was determined using Taqman®-probes-based PCRs contained 4 µl DNA template, 0.15 µl of the forward and reverse primer, 4µl TaqMan® Universal Master Mix and 4.3 µl double-distilled water in a total reaction volume of 12 µl with 95 °C for 10 min, followed by 40cycles of 95 °C for 15 min, and annealing at 60 °C for 60 min in Real-Time PCR System. The ABI-Step One instrument (Applied Biosystems) with SDS version-2.0 software was used for evaluating the genotypes.

Statistical Analysis

Data were analyzed using SPSS-20 software (SPSS Inc., IL, USA). Statistical analyzes of the difference between the frequencies of alleles and genotypes of the two groups were undertaken by Chi-square tests. Using logistic regression the relationship between genotype and disease was determined by estimating the OR (odds ratio) at 95% reliability. A T test was used to compare the parameters between the two groups. Clinical data are presented as means $\pm$ SD where appropriate for normally distributed variables or median and interquartile range for not normally distributed variables. The statistical analysis compares the average concentration difference of each of the inflammatory markers between the two groups using T test. The difference between subgroups was compared by the Chi-square test, and the relationship between markers and disease was estimated using logistic regression. The level of significance is ($P < 0.05$).

Results

Clinical Characteristics of the Population

Table 1 shows the characteristics of individuals with and without MetS. Body mass index (BMI), serum cholesterol, waist circumference (WC), fasting blood glucose (FBG), triglyceride (TG), low-density lipoprotein (LDL), systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were higher in people with MetS compared to those without MetS ($P < 0.05$), as may be expected. The serum high-density lipoprotein (HDL) level was significantly lower in subjects with MetS than in individuals without ($P < 0.05$).

Table 1 Comparison of the baseline characteristics between with or without MetS in obese group

Rs1800796	Mets − (control)	Mets + (cases)
Frequency (N %)		
Male	87 (68%)	70 (43.2%)
Female	41 (32%)	92 (56.8%)
Total	128 (100%)	162 (100%)*
Age (year)		
Male	57.37 ± 9.4	61.91 ± 3.8*
Female	53.56 ± 8.6	59.38 ± 5.2*
Waist circumference(cm)	96.2 ± 14.1	104.4 ± 8.3*
Height (m)	155 ± 8.2	159.7 ± 9.1*
HIPcircumference(cm)	104.94 ± 10.2	110.9 ± 8.2*
BMI (kg/m^2)	29.86 ± 5.1	32.8 ± 3.4*
Weight(kg)	73.64 ± 13.1	83.60 ± 10.8*
Fasting Blood Glucose(mg/dl)	87.86 ± 23.04	114.35 ± 55.9*
LDL-C (mg/dl)	116.64 ± 32.20	120.77 ± 37.93
HDL-C (mg/dl)	47.23 ± 9.61	39.19 ± 6.43*
Cholesterol (mg/dl)	195.3 ± 38.9	202.9 ± 46.3
Triglyceride (mg/dl)	108 (60)	161 (102.50)*
Hs-CRP (m/dl)	2.9 (5.5)	2.5 (4.4)*
Systolic blood pressure (mmHg)	121.9 ± 18.7	140.2 ± 19.1*
Diastolic blood pressure (mmHg)	78.6 ± 10.1	86.9 ± 9.5*

Mets syndrome metabolic, Values are expressed as mean ± SD, median and interquartile range for normally and non-normally distributed variables, respectively. *WC* waist circumference, *TC* total Cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *HC* hip circumference, *SBP*: systolic blood pressure, *DBP* diastolic blood pressure; *P value < 0.05. Chi-square and T test were used for continuous and categorical variables

Association of SNP rs1800796 with Mets and Its Components

We analyzed the association of rs1800796 with MetS in different genetic models, co-dominant, dominant, recessive and over-dominant. In order to investigate an association between Il-6-associated genetic-variant (rs1800796) with Mets, genotyping was done, and in all the samples genotyping was successfully performed and the polymorphism was consistent with the Hardy–Weinberg equilibrium. The frequency of the G allele in non-Mets group75.3% and in the MetS group was 67.7%, respectively. The frequency of the C allele in the non-MetS group was 24.4% and in MetS group was 32.3%. The association of polymorphism with MetS in four genetic models was studied, but no significant association was found (Tables 2, 3). The frequency of the GG, GC and CC in the non-MetS group and in the MetS group is presented in Fig. 1. The effect of sex, age and BMI were corrected for, and again, with four genetic models, the relationship

Table 2 Genotype frequencies for the rs1800796in Mets and controls in genetic models

Models	SNP Rs1800796	Frequencies for the IL6 SNP		Odds ratio (95% CI)	P
		Control	MetS		
Codominant	GG, no. (%)	52 (44.4%)	31 (46.3%)	Abate et al. (2016)	
	CG, no. (%)	60 (51.3%)	31 (46.3%)	1.13 (0.68–1.87)	0.64
	CC, no. (%)	5 (4.3%)	5 (7.5%)	2.43 (0.82–7.2)	0.108
Dominant	GG, no. (%)	53 (46.1%)	61 (40.9%)	Abate et al. (2016)	0.403
	CC/GC, no. (%)	62 (53.9%)	88 (59.1%)	1.23 (0.76–2.02)	
Recessive	GG/CG, no. (%)	110 (95.7%)	135 (90.6%)	Abate et al. (2016)	0.124
	CC, no. (%)	5 (4.3%)	14 (9.4%)	2.28 (0.8–6.53)	
Overdominant	GG/CC, no. (%)	58 (50.4%)	75 (50.3%)	Abate et al. (2016)	0.99
	CG, no. (%)	57 (49.6%)	74 (49.7%)	1.004 (0.62–1.63)	
Allele N,%	HWE	> 0.05	> 0.05	> 0.05	
	G	163 (70.9)	196 (65.8)	Abate et al. (2016)	
	C	67 (29.1)	102 (34.2)	1.27 (0.87–1.84)	0.214

Ref cat reference category, *CI* confidence interval

Logistic regression analysis was used to calculate the association of polymorphism and metabolic syndrome

Table 3 Comparison of the baseline characteristics in the recessive genetic model

RS1800796	Genotype (GC/GG)	Genotype (CC)
Sex (*n* %)		
Male	134 (54.9)	8 (42.1)
Female	110 (45.1)	11 (57.9)
Age (year)	58.36 ± 7.69	61.63 ± 2.97
Waist circumference(cm)	101.95 ± 12.14	104.13 ± 12.38
HIP circumference(cm)	108.22 ± 9.76	110.36 ± 7.45
BMI (kg/m^2)	31.55 ± 4.54	32.21 ± 1.77
Fasting Blood Glucose(mg/dl)	102.87 ± 45.59	101.05 ± 41.70
LDL-C (mg/dl)	119.29 ± 37.59	130.91 ± 41.95
HDL-C (mg/dl)	43.05 ± 9.96	39.47 ± 11.24
Cholesterol (mg/dl)	199.32 ± 42.39	207.79 ± 44.35
Triglyceride (mg/dl)	133 (80)	163 (85)
Hs-CRP (m/dl)	2.82 (142.68)	2.57 (77.82)
Systolic blood pressure (mmHg)	131.99 ± 20.99	135.56 ± 20.19
Diastolic blood pressure (mmHg)	83.14 ± 10.57	87.70 ± 10.47

MetS metabolic syndrome, values are expressed as mean ± SD, median and interquartile range for normally and non-normally distributed variables, respectively. *WC* waist circumference, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *HC* hip circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure; *$P < 0.05$. Chi-square and T test were used for continuous and categorical variables
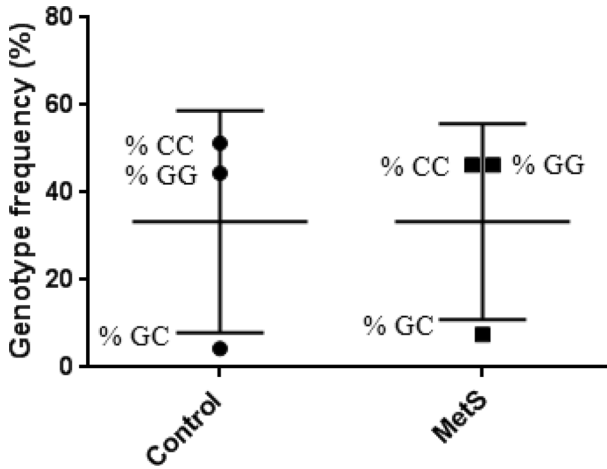
Fig. 1 Genotypes frequency in the MetS and control groups

Table 4 Relationship between genotype and metabolic syndrome components

Rs1800796	Genotype (GC/GG)	Genotype (CC)	Odds ratio (95% CI)	P
BMI (kg/m^2)	31.55 ± 4.54	32.21 ± 1.77	1.54 (1.04–2.29)*	0.031
LDL-C (mg/dl)	119.29 ± 37.59	130.91 ± 41.95	1.01 (0.97–1.05)*	0.037
HDL-C (mg/dl)	43.05 ± 9.96	39.47 ± 11.24	0.89 (0.81–0.97)*	0.010

Values are expressed as mean ± SD for normally distributed variables

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol; *$P < 0.05$. Logistic regression analysis was used to calculate the association of polymorphism and MetS components

between polymorphism and Mets was examined. The relationship between polymorphism and MetS features was also investigated. There was a significant association between the rs1800796 polymorphism with BMI ($P = 0.031$) in the genetic recessive model. Also, there was a significant association with HDL-cholesterol ($P = 0.010$) and LDL-cholesterol ($P = 0.037$) (Table 4), while the relationship between polymorphism and other MetS features was not significant (Supplementary Table).

Discussion

We found that there was a significant relationship between the CC genotype of rs1800796 polymorphism and increased BMI ($P = 0.031$) as well as with decreased levels of HDL ($P = 0.010$) as well as with increased levels of LDL ($P = 0.037$) in MetS subjects using a recessive genetic model, but there was no significant relationship between rs1800796 polymorphism and MetS. Some

other studies have also reported no association between this polymorphism (rs1800796), with Mets and disorders associated with Mets such as type 2 diabetes and cardiovascular disease (Huth et al. 2006; Sun et al. 2014). Additionally, Sun et al. investigated the relationships between polymorphisms of the interleukin IL-6 gene 174 G > C (rs1800795), 572 G > C (rs1800796) and 597 G/A (rs1800797) with CAD risk in a Chinese population. They found that the IL-6 174CC genotype was associated with a significantly increased risk of CAD compared to the wild-type GG genotype in a codominant model, whereas IL-6 174 G > C polymorphism presented an increased risk of CAD in dominant and recessive models. However, they did not find that the IL-6 572 CC and 597 AA genotypes were correlated with an increased risk of CAD (Sun et al. 2014). Several lines of evidence indicate a causal role of the cytokine interleukin (IL)-6 in the development of type 2 diabetes in humans. Two common polymorphisms in the promoter of the IL-6 encoding gene IL6, -174G > C (rs1800795) and -573G > C (rs1800796), have been investigated for association with type 2 diabetes in numerous studies but with results that have been largely equivocal. The diplotypers 1800796 G/*-rs2097677 A/* might contribute to responsiveness to DPP-4Is) dipeptidyl peptidase-4 inhibitors (in Japanese patients with type 2 diabetes (Matsui et al. 2015). The study presented that IL-6 gene polymorphisms, rs1800796 and rs1524107, may serve as predictors of progression of nephropathy in Chinese patients with type 2 diabetes (Chang et al. 2016). Moreover, Huth C et al. in their research didn't find evidence for an association between IL6 -573G > C and type 2 diabetes (Huth et al. 2006). In the type 2 diabetes mellitus group, IL6-174CC carriers showed higher concentrations of glycated hemoglobin, albumin-to-creatinine ratio, total cholesterol and LDL-cholesterol, when compared with GG + GC genotype carriers (Ururahy et al. 2015).

On the other hand, Karaman E et al. found the relationship -572 G/C genetic variants among neither IL-6 and CRP levels nor hypertension in a Turkish population (Karaman et al. 2015), while Fernandes MT et al. found the rs1800796-572G/C IL6 is a protective agent for the attendance and intensity of hip and knee osteoarthritis in the aged (Fernandes et al. 2015). Zhang X et al. reported that genetic variants in interleukin-6 can modify the risk of obstructive sleep apnea syndrome. However, in non-obese individuals ($n = 117$), the minor allele G (rs1800796) decreased risk of OSAS compared with the major allele C [odds ratio (OR), 0.48; 95% confidence interval (CI), 0.26–0.86; $P = 0.014$], and the haplotype TG (rs1880242, rs1800796) conferred a significantly decreased risk of OSAS than single allele G (rs1800796) (OR, 0.39; 95% CI 0.20–0.74; $P = 0.003$). Moreover, the severity of sleep-disordered breathing (measured by apnea–hypopnea index) increased linearly in carriers of the C variant of IL-6-572G/C polymorphism (14.3 ± 5.1, 22.0 ± 3.6 and 34.8 ± 3.5 for GG, CG and CC, respectively; $P = 0.012$) (Zhang et al. 2009).

So far, the effect of various genetic factors on metabolic syndrome has been studied. For example, in a study of 378 Thai populations, the association between cholesterol ester transfer protein (CETP) TaqIB and apolipoprotein E (ApoE)

polymorphism in both groups with and without metabolic syndrome was investigated. The results of this study did not show a significant association between these two polymorphisms and metabolic syndrome in the Thai population (Jeenduang et al. 2015).

The relationship between inflammatory proteins with metabolic syndrome and cardiovascular disease has been studied in the past. For example, a study was conducted on two groups of cardiovascular patients and healthy subjects. The results of this study failed to provide evidence that IL-6 promoter region polymorphisms play a role in the pathogenesis of cardiovascular disease. But the results indicate that IL-6 is one of the risk factors for these types of diseases in men (Bennet et al. 2003). A study done on 1028 people showed that there is a significant association between the polymorphism rs1800795 of the IL-6 gene and insulin resistance and BMI in obese people (Underwood et al. 2012). A study on a group of obese women examined the association of a number of polymorphisms with obesity. One of these polymorphisms is the same as polymorphism in our study. The results of this report indicate that there is no significant difference in the frequency of rs1800796 polymorphism between the obese and control groups. But obese people have higher levels of primary DNA damage (Hasnain 2015). Also, a study in Chile examined the association between some polymorphisms such as IL-6 (rs1800796) with obesity in obese children aged 10 ± 2 years. This study was conducted on 259 participants of 26.1 ± 4.1 kg/m^2. The results show that there is no significant association between any of the IL-6 polymorphisms with MetS. However, the polymorphisms studied from IL-18 (rs360719-rs187238-rs204355) showed an association with TG $\leq$ 110 mg/dL and HDL $<$ 40 mg/d (Suazo et al. 2014).

In a study of 301 adults, the effect of genetics on the fatty acids associated with the risk of metabolic syndrome has been studied. The results of this study indicate one of the genotypes of IL-6 SNP (rs1800795 G alleles); it has a significant risk of developing metabolic syndrome. These individuals have higher levels of inflammatory factors such as IL-6, TNF-a and CRP, lower levels of adiponectin, and have metabolic abnormalities in fatty acids (Norde et al. 2018). There is a growing body of data showing the association between interleukin-6 middle levels with risk factors for coronary artery disease (CAD) including LDL, oxidized LDL and with the degree of oxidation. Studies have shown that therapy of human microvascular endothelial cells-1 with increasing doses of interleukin-6 significantly raised LDL receptor and oxidized lipoprotein receptor-1 mRNA expression (Lubrano et al. 2015 .Interleukin-6 (IL-6), an inflammatory cytokine, is considered a candidate gene possibly involved in susceptibility to nephropathy in diabetes. In general terms, the IL-6 polymorphism genotypes were Essentially associated with inflammatory cytokines, while the IL-6R polymorphism genotypes were associated with anti-inflammatory cytokines (Mitrokhin et al. 2017).

Table 5 Genotype frequencies for the rs1800796 in codominant models in several studies

Models	SNP Rs1800796 (IL-6 572G > C polymorphism)	Frequencies for the IL6 SNP					References
		Control	MetS	Insulin resistance	Hypertension	Coronary syndromes	
Codominant	GG (%)	44.40%	46.30%	–	–	–	Results of present study
	CG (%)	51.30%	46.30%	–	–	–	
	CC (%)	4.30%	7.50%	–	–	–	
Codominant	GG (%)	91.80%	–	91.20%	91.40%	–	Dandona et al. (2004)
	CG (%)	7.70%	–	8.40%	8.30%	–	
	CC (%)	0.50%	–	0.40%	0.20%	–	
Codominant	GG (%)	44%	–	–	–	41%	Wang et al. (2016)
	CG (%)	42%	–	–	–	51%	
	CC (%)	15%	–	–	–	8%	

Teixeira et al. reviewed the association between another polymorphism (IL-6-174G/C gene polymorphism) with MetS. This study was conducted on people with high blood pressure. The results show that the G/G carrier was more common in all groups and increased the prevalence of MetS in the C carrier group compared to the GG group. Also, the C carrier group showed higher levels of BMI, WC, VLDL-C and lower HDL-C and APO-A levels (Teixeira 2015).

Our recent results also presented that this emerging marker was not associated with MetS. In particular, we showed that MetS group with the GG/GC genotypes had a high level of HDL (0.037) as well as low level of LDL (0.010) and BMI (0.031) in the recessive genetic model. The minor allele frequency of rs1800796 in project of 1000 Genomes, TOPMED and GnomAD is C=0.3139, C=0.1293 and C=0.1054, while in this study frequency of allele C is reported 0.3 and 0.2 in case and control, respectively. Moreover, this polymorphism had a frequency of 46.1%, 49.6% and 4.3% for GG, CG and CC, respectively in the control group, while these frequencies in the case group were 40.9%, 49.7%, and 9.4% for GG, CG and CC. Also, these frequencies in Mexican population were 41%, 51% and 8% for GG, CG and CC, respectively, in patients with acute coronary syndromes and 44%, 42% and 15% for GG, CG and CC in healthy controls (Fragoso et al. 2010) (Table 5). Some studies investigated the relationship between different genetic factors and MetS in the Iranian population. For example, Ghazizadeh et al. found a significant association between genetic-polymorphism, rs10738760 of vascular endothelial growth factor with MetS in 850 participants from an Iranian population (Ghazizadeh et al. 2017). The main limitation is age and sex differences between groups, although these variables were adjusted in the logistic regression model. Next limitations are the small samples size and cross-sectional study design. However, it is possible that lifestyle features have an effect on the correlation between polymorphism with MetS and its components.

Conclusion

To the best of our knowledge, this is the first study presenting the association of a genetic variant of IL6, rs1800796 with risk of MetS such as with increased levels of LDL and BMI as well as with reduced HDL level. Supporting further studies needs to assay this association in a larger population.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abate M, Salini V, Andia I (2016) How obesity affects tendons? Adv Exp Med Biol 920:167–177

Ahmadnezhad M, Arefhosseini SR, Parizadeh MR, Tavallaie S, Tayefi M, Darroudi S et al (2018) Association between serum uric acid, high sensitive C-reactive protein and pro-oxidant-antioxidant balance in patients with metabolic syndrome. BioFactors 44:263

Alexopoulos AS, Fayfman M, Zhao L, Weaver J, Buehler L, Smiley D et al (2016) Impact of obesity on hospital complications and mortality in hospitalized patients with hyperglycemia and diabetes. BMJ Open Diabetes Res Care 4(1):e000200

Almeida DCd. Alterações genéticas relacionadas à obesidade: danos no DNA, perfil de expressão e polimorfismos gênicos. 2013.

Bagherniya M, Khayyatzadeh SS, Avan A, Safarian M, Nematy M, Ferns GA et al (2017) Metabolic syndrome and its components are related to psychological disorders: a population based study. Diabetes Metab Syndr 11(Suppl 2):S561–S566. https://doi.org/10.1016/j.dsx.2017.04.005

Bennet AM, Prince JA, Fei G-Z, Lyrenäs L, Huang Y, Wiman B et al (2003) Interleukin-6 serum levels and genotypes influence the risk for myocardial infarction. Atherosclerosis. 171(2):359–367

Bhatheja S, Panchal HB, Ventura H, Paul TK (2016) Obesity cardiomyopathy: pathophysiologic factors and nosologic reevaluation. Am J Med Sci 352(2):219–222

Chang W-T, Huang M-C, Chung H-F, Chiu Y-F, Chen P-S, Chen F-P et al (2016) Interleukin-6 gene polymorphisms correlate with the progression of nephropathy in Chinese patients with type 2 diabetes: a prospective cohort study. Diabetes Res Clin Pract 120:15–23

Dandona P, Aljada A, Bandyopadhyay A (2004) Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 25(1):4–7

Du Y, Gao L, Zhang K, Wang J (2015) Association of the IL6 polymorphism rs1800796 with cancer risk: a meta-analysis. Genet Mol Res. 14:13236–13246

Fernandes MT, Fernandes KB, Marquez AS, Cólus IM, Souza MF, Santos JPM et al (2015) Association of interleukin-6 gene polymorphism (rs1800796) with severity and functional status of osteoarthritis in elderly individuals. Cytokine 75(2):316–320

Ferrara N, Gerber H-P, LeCouter J (2003) The biology of VEGF and its receptors. Nat Med 9(6):669–676

Fragoso JM, Delgadillo H, Juárez-Cedillo T, Rodríguez-Pérez JM, Vallejo M, Pérez-Méndez O et al (2010) The interleukin 6–572 G%3e C (rs1800796) polymorphism is associated with the risk of developing acute coronary syndrome. Genet Test Mol Biomark 14(6):759–763

Galassi A, Reynolds K, He J (2006) Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 119(10):812–819

Gato WE, Hunter DA, Whitby SL, Mays CA, Yau W (2016) Investigating susceptibility to diabetes using features of the adipose tissue in response to in utero polycyclic aromatic hydrocarbons exposure. Diabetes Metab J 46:494

Ghazizadeh H, Fazilati M, Pasdar A, Avan A, Tayefi M, Ghasemi F et al (2017) Association of a vascular endothelial growth factor genetic variant with serum VEGF level in subjects with metabolic syndrome. Gene 598:27–31

Ghazizadeh H, Avan A, Fazilati M, Azimi-Nezhad M, Tayefi M, Ghasemi F et al (2018) Association of rs6921438 A%3c G with serum vascular endothelial growth factor concentrations in patients with metabolic syndrome. Gene 667:70–75

Hamid Y, Rose C, Urhammer S, Glümer C, Nolsøe R, Kristiansen O et al (2005) Variations of the interleukin-6 promoter are associated with features of the metabolic syndrome in Caucasian Danes. Diabetologia 48(2):251–260

Hasnain S (2016) Obesity, more than a 'cosmetic' problem Current knowledge and future prospects of human obesity genetics. Biochem Genet 54(1):1–28

Huth C, Heid IM, Vollmert C, Gieger C, Grallert H, Wolford JK et al (2006) IL6 gene promoter polymorphisms and type 2 diabetes joint analysis of individual participants' data from 21 studies. Diabetes 55(10):2915–2921

Jeenduang N, Porntadavity S, Nuinoon M, Horpet D, Thepkwan N, Thaworn P et al (2015) Studies of the CETP TaqIB and ApoE polymorphisms in Southern Thai subjects with the metabolic syndrome. Biochem Genet 53(7–8):184–199

Karaman E, Kucuk MU, Bayramoglu A, Göçmen SU, Ercan S, Guler HI et al (2015) Investigation of relationship between IL-6 gene variants and hypertension in Turkish population. Cytotechnology 67(6):947–954

Lau C-H, Muniandy S (2013) Influence of adiponectin and resistin gene polymorphisms on quantitative traits related to metabolic syndrome among Malay, Chinese, and Indian men in Malaysia. Biochem Genet 51(1–2):166–174

Lubrano V, Gabriele M, Puntoni MR, Longo V, Pucci L (2015) Relationship among IL-6, LDL cholesterol and lipid peroxidation. Cell Mol Biol Lett 20(2):310–322

Matsui M, Takahashi Y, Takebe N, Takahashi K, Nagasawa K, Honma H et al (2015) Response to the dipeptidyl peptidase-4 inhibitors in Japanese patients with type 2 diabetes might be associated with a diplotype of two single nucleotide polymorphisms on the interleukin-6 promoter region under a certain level of physical activity. J Diabetes Investig 6(2):173–181

Mirhafez SR, Pasdar A, Avan A, Esmaily H, Moezzi A, Mohebati M et al (2015) Cytokine and growth factor profiling in patients with the metabolic syndrome. Br J Nutr 113(12):1911–1919

Mitrokhin V, Nikitin A, Brovkina O, Khodyrev D, Zotov A, Vachrushev N et al (2017) Association between interleukin-6/6R gene polymorphisms and coronary artery disease in Russian population: influence of interleukin-6/6R gene polymorphisms on inflammatory markers. J Inflam Res 10:151

Norde MM, Oki E, Carioca AAF, Damasceno NRT, Fisberg RM, Marchioni DML et al (2018) Influence of IL1B, IL6 and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study. Clin Nutr 37(2):659–666

Park HS, Park JY, Yu R (2005) Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-α and IL-6. Diabetes Res Clin Pract 69(1):29–35

Pérez AP, Munoz JY, Cortés VB, de Pablos Velasco P (2007) Obesity and cardiovascular disease. Public Health Nutr. 10(10A):1156–1163

Ponnana M, Sivangala R, Joshi L, Valluri V, Gaddam S (2017) IL-6 and IL-18 cytokine gene variants of pulmonary tuberculosis patients with co-morbid diabetes mellitus and their household contacts in Hyderabad. Gene 627:298–306

Rafiq S, Frayling T, Murray A, Hurst A, Stevens K, Weedon M et al (2007) A common variant of the interleukin 6 receptor (IL-6r) gene increases IL-6r and IL-6 levels, without other inflammatory effects. Genes Immun 8(7):552

Sirdah MM, Ghali ASA, Al Laham NA (2012) The reliability of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III) and the International Diabetes Federation (IDF) definitions in diagnosing metabolic syndrome (MetS) among Gaza Strip Palestinians. Diabetes Metab Syndr 6(1):4–8

Slattery ML, Wolff RK, Herrick JS, Caan BJ, Potter JD (2007) IL6 genotypes and colon and rectal cancer. Cancer Causes Control 18(10):1095–1105

Slattery ML, Curtin K, Sweeney C, Wolff RK, Baumgartner RN, Baumgartner KB et al (2008) Modifying effects of IL-6 polymorphisms on body size-associated breast cancer risk. Obesity. 16(2):339–347

Stephenson GD, Rose DP (2003) Breast cancer and obesity: an update. Nutr Cancer 45(1):1–16

Suazo J, Smalley S, Hodgson M, Weisstaub G, Gonzalez A, Santos J (2014) Association between genetic polymorphisms of interleukin 6 (IL6), IL6R and IL18 with metabolic syndrome in obese Chilean children. Rev Med Chil 142(3):290–298

Sun G, Wu G, Meng Y, Du B, Li Y (2014) IL-6 gene promoter polymorphisms and risk of coronary artery disease in a Chinese population. Genet Molec Res. 13:7718–7724

Sun H, Ren X, Chen Z, Li C, Chen S, Wu S et al (2016) Association between body mass index and mortality in a prospective cohort of Chinese adults. Medicine 95(32):e4327

Teixeira AA, Quinto BMR, Dalboni MA, Rodrigues CJdO, Batista MC (2015) Association of IL-6 polymorphism -174G/C and metabolic syndrome in hypertensive patients. BioMed Res Int 2015:6

Timasheva Y, Nasibullin T, Zakirova A, Mustafina O (2008) Association of interleukin-6, interleukin-12, and interleukin-10 gene polymorphisms with essential hypertension in Tatars from Russia. Biochem Genet 46(1–2):64–74

Underwood PC, Chamarthi B, Williams JS, Sun B, Vaidya A, Raby BA et al (2012) Replication and meta-analysis of the gene-environment interaction between body mass index and the interleukin-6 promoter polymorphism with higher insulin resistance. Metabolism. 61(5):667–671

Ururahy MAG, Souza KSC, Oliveira YMdC, Loureiro MB, Silva HPV, Freire-Neto FP et al (2015) Association of polymorphisms in IL6 gene promoter region with type 1 diabetes and increased albumin-to-creatinine ratio. Diabetes/Metab Res Rev 31(5):500–506

Wang Z, Wu S, Liao J, Zhong L, Xing T, Fan J et al (2016) Interleukin-6 and rs1800796 locus single nucleotide polymorphisms in response to hypoxia/reoxygenation in hepatocytes. Int J Mol Med 38(1):192–200

Zhang X, Liu R-Y, Lei Z, Zhu Y, Huang J-A, Jiang X et al (2009) Genetic variants in interleukin-6 modified risk of obstructive sleep apnea syndrome. Int J Mol Med 23(4):485

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