Biomedical Research 2017; 28 (2): 508-511 *ISSN 0970-938X*
www.biomedres.info

IGF2BP2 gene polymorphism in patients with morbid obesity.

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Abstract

Background/Aim: In this study, it was aimed to determine the relationship between morbid obesity and insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) rs1470579 and rs4402960 gene polymorphisms.
Materials and methods: Data from 100 consecutive patients who underwent surgery due to morbid obesity (MO) and 100 healthy volunteers with normal body mass index (BMI) were compared. DNAs obtained from blood samples were analysed by real-time polymerase chain reaction (PCR) for rs1470579 and rs4402960 gene polymorphisms.
Results: While there were 62 (62%) female and 38 (38%) male patients, the healthy control group consisted of 57 (57%) women and 43 (43%) men. The mean ages of morbidly obese patients and healthy individuals were 41.2 ± 7.8 (median=39, min=17, max=58) and 36.9 ± 6.5 (median=37, min=20, max=51), respectively ($p>0.05$). The mean BMI of obesity and control groups were 44.9 ± 11.2 and 23.2 ± 2.7, respectively ($p<0.05$). No significant differences were found between morbidly obese patients and healthy individuals regarding IGF2BP2 rs1470579 and rs4402960 gene polymorphisms and allele frequencies ($p>0.05$).
Conclusion: No significant differences were found between morbidly obese patients and healthy individuals regarding IGF2BP2 rs1470579 and rs4402960 gene polymorphisms and allele frequencies.

Keywords: IGF2BP2, Morbidly obese, rs1470579, rs4402960.

Accepted on May 05, 2016

Introduction

Obesity, which is accepted as one of the most risky 10 diseases by World Health Organization (WHO), is a major health problem that can lead to various disorders and even can cause death by affecting all organs and systems of the body, especially cardiovascular and endocrine system [1]. Morbid obesity (MO) is usually defined as a BMI of ≥ 40 kg/m^2 or ≥ 35 kg/m^2 and experiencing obesity-related comorbidities (type 2 diabetes, hypertension, sleep apnea, and hyperlipidemia). Surgery is one of the treatment methods in MO [2].

Previous studies provided evidence for gene-obesity interaction in human complex disease [3-5]. Various genetic results have been obtained regarding obesity and related diseases. However, no major gene was detected that played role in the development of obesity in these studies. Therefore, the number of studies investigating the genetic basis of obesity is increasing every day. One of the genes that are subject to studies on obesity and genetic is related to IGF2 and species. Studies also supported the assumption that IGF2 was strongly associated with obesity [6]. IGFBP-2 has been shown to have protective effect against obesity and insulin resistance in rats [7]. But, some IGF2BP2 variants have been found to be associated with obesity and type 2 DM [8,9].

IGF2BP2 is encoded by the IGF2BP2 gene, which is located on chromosome 3q27. Its strong association with β cell function is established by regulating IGF2 post-translation [10]. IGF2BP2 is a RNA-binding factor that recruits target transcripts to cytoplasmic protein-RNA complexes (mRNPs). This transcript 'caging' into mRNPs allows mRNA transport and transient storage. It also modulates the rate and location at which target transcripts encounter the translational apparatus

and shields them from endonuclease attacks or microRNA-mediated degradation (By similarity). It functions by binding to the 5'-UTR of the insulin-like growth factor 2 (IGF2) mRNAs. Binding is isoform-specific. It binds to beta-actin/ACTB and MYC transcripts [10]. IGF2BP2 gene, insulin-like growth factor (IGF2), is stated to be involved in growth, development, cell differentiation and metabolism [11]. IGF system is composed of different groups: IGF-1, IGF-2, IGF binding proteins (IGFBP) and IGF receptors (IGFR) [12,13]. IGF2BP2, which is a member of mRNA binding protein family, that has functions related with RNA localization, stability and translation [14]. IGF2BP2 plays role in the regulation of translation of insulin-like growth factor 2 (IGF2) by binding to 5 'UTR region of IGF2 mRNA [15]. The IGF2BP2 gene, located on chromosome 3q27.2, spans about 181.3 kb with 16 exons [16]. As known, this gene encodes a member of IGF-II mRNA-binding proteins (IMP). The protein encoded by this gene has been have been reported to include several KH and RRM effects. Alternative transcriptional splice variant has been characterized by the form that is encoding a different isoform [17].

In this study, it was aimed to identify the relationship between morbid obesity in Turkey and IGF2BP2 rs1470579 and rs4402960 gene polymorphisms.

Materials and Methods

The study protocol was approved by the institutional ethics committee. An informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Helsinki Declaration. Hundred consecutive patients who underwent surgery due to morbid obesity and age and gender-matched 100 healthy volunteers with normal body mass index (BMI) were included in the study.

A venous blood sample of 2-3 mL was drawn from all participants and put into tubes with ethylenediaminetetraacetic acid (EDTA). Deoxyribonucleic acid (DNA) isolations were done in Medical Genetics Laboratory using the DNA isolation kit (PureLink™ genomic DNA kits, Invitrogen, Carlsbad, CA 92008 USA). Isolated DNAs were stored at -20°C until the analyses were performed. Genotyping was performed with Applied Biosystems™ Real-Time PCR Instruments StepOne Plus Real Time Polymerase Chain Reaction (PCR) equipment (Applied Biosystems, Foster City, CA, USA) [18].

The primers belonging to identified-rs of IGF2BP2 gene were designed and identified polymorphisms in the respective gene regions were investigated by real-time polymerase chain reaction (Real Time PCR) method as mentioned in Table 1. In this study, single point mutation (SNP) scans were analyzed with appropriate sets of primers and probes by duplicating target areas in patients and controls. Micro-volume spectrophotometer was used to measure the purity and quantity of DNAs belonging to isolated samples. The study was checked with appropriate equipment in each stage using ready-to-use mastermix kits for quantitative PCR amplification and Real Time PCR instrument for analysis. By using wild-type sequence and gene mutation groups for involved gene, alleles of the genes that give rise to different properties due to carrying different codes although encoding the same characteristic property were determined by Taqman probes.

Statistical analysis

Statistical Package for the Social Sciences (SPSS 21, Chicago, IL, USA) statistical software was used for the analysis of data. Student's t-test was used for comparison of the groups. Quantitative variables were expressed as mean ± standard deviation. Categorical variables were expressed as number (n) and percentage (%). Stability control of the study population was detected by Hardy-Weinberg equilibrium and Chi-square test after determining gene frequency of each allele. All the hypotheses were constructed as two-tailed and an alpha critical value of 0.05 was accepted as significant.

Results

There were 62 (62%) female and 38 (38%) male patients in the patient group. The control group consisted of 57 (57%) women and 43 (43%) men. The mean ages of obese patients and healthy individuals were 41.2 ± 7.8 and 36.9 ± 6.5 years, respectively ($p>0.05$). Mean body mass index (BMI) values in the obesity group and control group were 44.9 ± 11.2 and 23.2 ± 2.7, respectively and both groups were significantly different ($p<0.05$). In addition, belly and thigh circumferences by gender were also significantly different ($p<0.01$). General characteristics of the study population are shown in Table 2.

There were no relationships between morbidly obese patients and healthy individuals regarding IGFBP2 rs1470579 and rs4402960 gene polymorphisms. Genotype comparisons associated with rs1470579 and rs4402960 gene polymorphisms are presented in Table 3.

Table 1. *Primary sequences used for IGF2BP2 gene regions.*

A-T switching	rs1470579 (A) P1	CATACGAGTT [A] ATCCTGCCT
	rs1470579 (T) P2	CATACGAGTT [T] ATCCTGCCT
G-T switching	rs4402960 (G)-P1	ACAGTAGATT [G] AAGATACTGATT
	rs4402960 (T)-P2	ACAGTAGATT [T] AAGATACTGATT

Table 2. *General characteristics of study participants.*

	Morbidly obese	Healthy control	p
N (K/E)	100 (62/38)	100 (57/43)	>0.05
Age (years)	41.2 ± 7.8	36.9 ± 6.5	>0.05
BMI	44.9 ± 11.2	23.2 ± 2.7	<0.05
FBC (cm) Mean ± SD	136.59 ± 8.8	77.04 ± 9.04	<0.01
FHC (cm) Mean ± SD	156.3 ± 9.64	80.45 ± 8.9	<0.01
MBC (cm) Mean ± SD	150.44 ± 5.47	86.9 ± 7.1	<0.01
MHC (cm) Mean ± SD	124.5 ± 2.8	95.85 ± 4.8	<0.01

FBC: Female Belly Circumference; FHC: Female Hip Circumference; MGC: Male Belly Circumference; MHC: Male Hip Circumference.

Table 3. *Distribution of rs1470579 and rs4402960 genotypes and alleles in the patient and control groups.*

	Genotype Allele	Patient (n=100)	Control (n=100)	X^2	P
rs1470579	AA	33 (0.33)	22 (0.22)	3.61	0.16
	AT	12 (0.12)	18 (0.18)		
	TT	55 (0.55)	60 (0.60)		
	A	78 (0.39)	62 (0.31)	2.81	0.09
	T	122 (0.61)	138 (0.69)		
rs4402960	GG	51 (0.51)	58 (0.58)	2.34	0.12
	GT	11 (0.11)	12 (0.12)		
	TT	38 (0.38)	30 (0.30)		
	G	113 (0.565)	128 (0.64)	1.43	0.48
	T	87 (0.435)	72 (0.36)		

Discussion

Besides causing social psychological problems, morbid obesity is associated with many important diseases such as hypertension, cardiovascular diseases, diabetes, degenerative arthritis, thrombophlebitis and it has been found to reduce life expectancy [1,19]. Many genetic studies have been conducted on the role of IGF2 and other products in obesity. Strong association between IGF2 and obesity was reported in the studies [6]. However, different results were obtained in studies demonstrating the relationship between IGFBP and obesity. Although Wheatcroft et al. [7] reported that IGFBP-2 had protective effect against obesity and insulin resistance in rats, some IGF2BP2 variants have been found to be associated with obesity and type 2 DM [8,9].

In 2015, Lebedy et al. investigated the relationship between type 2 DM and IGF2BP2 in Egypt and determined a significant association between T2DM and IGF2BP2 variants rs4402960 and rs1470579 in Egyptians [20]. In a study in 2015 on the relationship between obesity and IGF2R gene, Yhang et al. [21] showed that IGF2R rs629849 might influence the development of obesity in Korean population. Similarly, in their study comparing 281 type 2 DM patients and 111 healthy volunteers in 2014, Zhang et al. [22] determined that type 2 DM was associated with IGF2BP2 gene rs1470579 and rs4402960 polymorphisms in Chinese population. But, in a study with a total of 2,301 obese Chinese Han subjects, Wu et al. [23] found no relationship between type 2 DM and IGF2BP2 (rs4402960) gene, but reported that IGF2BP2 (rs4402960) had a protective effect against type 2 DM in obese subjects. In our study, we found no statistically significant difference between morbidly obese patients and non-obese healthy individuals in terms of IGF2BP2 gene rs1470579 and rs4402960 gene polymorphisms and allele frequencies. We believe that the difference between the study results is due to different allele frequencies varying according to species, race and the number of the study population.

In conclusion, no relationship was found between morbid obesity and IGFBP2 rs1470579 and rs4402960 gene polymorphisms in Turkey.

Study limitations

The limitations of our study are as follows: small number of patients included in the study, lack of specifying chronic diseases in patients, lack of mentioning other metabolic disorders such as insulin resistance and atherosclerosis that are associated with obesity, and different blood sampling times. As many factors play role and each metabolic condition affects the development of obesity, we believe that conducting obesity-related genetic studies in more isolated study groups will help in the diagnosis of genetic basis of obesity. Studies on isolated diseases are needed for this subject.

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