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Investigation of the Relationship between IL-6, IL-6R and CXCL5 Polymorphisms and Obesity in Denizli Province of Turkey

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Abstract

Obesity and its effects on increasing morbidity and mortality have reached the level of an epidemic with a high frequency in modern populations. *IL-6* released from adipose tissue is known to trigger the chronic inflammation in obesity. *CXCL5*, which mediates the activation and migration of neutrophils, has been found at high levels in obese subjects. In our study, we aimed to investigate the possible effects of *IL-6*, *IL-6R* and *CXCL5*, polymorphisms and haplotypes on the development of obesity. We studied *IL-6*, rs2069827 (-1363, G/T), rs1800797 (-597, G/A), rs1800796 (-572, G/C) and rs1800795 (-174, G/C), *IL-6R* rs4845617 (-183, G/A), rs2228145 (+48892, A/C) and *CXCL5* rs352046 (-156, G/C) polymorphic sites in 60 obesity patients and 59 healthy controls. For genotyping we used PCR-RFLP based approach. The *IL-6* rs1800796, rs1800795 and *IL-6R* rs4845617 G allelles could be the possible genetic factors responsible for obesity. We found similar results in female obese group. The results indicated that there was no association between obesity and other SNPs (rs2069827, rs1800797, and rs1800795 and rs2228145) and *CXCL5*, rs352046. The results of *IL-6* and *IL-6R* haplotype analysis by global differentiation test showed that haplotypes may have different distributions between obese and controls. Our results showed that polymorphisms and possible haplotypes in *IL-6* and *IL-6R* genes, which have an important role in inflammation, may affect the development of obesity. This study points out the necessity of investigating the possible effects of gene polymorphisms of other cytokines and their receptors in the development of obesity in larger populations.

Keywords

Obesity, IL-6, IL-6R, CXCL5, Haplotype

Introduction

Obesity, which is defined as the most important multifactorial, complex chronic disease of the 21st century has a prevalence of more than 20% in modern populations and reached the level of an epidemic (Hossain, 2007). The prevalence of obesity in Turkey has exceeded the critically high rate of 30%, and it is more prevalent in females. Studies in Eastern Turkey which covered our region have found similar prevalence of obesity and overweight rates (Sevinç, 2011; Yilmaz, 2019). Obesity has been found to be associated with an increased risk of premature death due to a significantly increased risk of developing diabetes, hypertension, coronary heart disease, stroke and several types of cancer (Yao, 2014).

Although the factors that cause obesity are not clearly known, it is accepted that genetic and environmental factors, together with overnutrition and insufficient physical activity, are important in the development of obesity (Chavey, 2009a). It is widely accepted that immune system failures are major contributors to the development of obesity-related changes, particularly inflammation and insulin resistance. Altered levels of circulating inflammatory cytokines such as TNFα, IL-1, IL-6, or C-reactive protein (CRP) have been reported in overweight and obese adults. This is associated with the concomitant development of insulin resistance, metabolic disorders and the increased cardiovascular risks seen in obesity (Yao, 2014; Wang and He, 2018; Ghanbari, 2021). High levels of inflammatory cytokines such as TNF-alpha and IL-6 are secreted by the adipose tissue macrophages, and these trigger chronic inflammation by stimulating the production of CRP in the liver (Weisberg, 2003). Measurements have been shown to correlate positively with serum levels of inflammatory proteins such as IL-6 in obese patients (Ma, 2019).

IL-6, a proinflammatory cytokine that functions by binding to the IL-6 receptor in various cells, have been shown to be responsible in several immune-related disorders such as rheumatoid arthritis, multiple sclerosis, Behçet's disase, diabetes or cancer (Chang, 2005; Zavaleta-Muniz, 2013; Tala, 2021). The action of IL-6 is mediated through receptor of IL-6 (IL-6R) and generally accepted that serum levels of IL-6 and IL-6R together increases with obesity and diabetes (Bustamante, 2007). The studied SNP regions of IL-6R, s4845617 (-183, G/A) (in promoter region) and rs2228145 (+48892, A/C) (in exon 4) were reported to be important for their potent on serum levels of IL-6R (Galicia, 2004). The studies in different diseases such as rheumatoid arthritis, systemic lupus erythematosus, chronic perionditidis, cancer, metabolic syndrome or diabetes suggested that further studies and analysis of *IL-6* and *IL-6R* polymorphisms need to confirm the relationships with disease progressions (Chang, 2005; Qi, 2009; Jeon, 2013; Zhang, 2014; Huang, 2020). Studies have shown that *CXCL5* (ENA-78, epithelial-neutrophil activating peptide-78) is a new chemokine secreted by macrophages located in adipose tissue and that circulating *CXCL5* is highly increased during the development of obesity in humans (Chavey, 2009b). It is emphasized that the rs352046 locus located in the promoter region may be involved in the expression of *CXCL5* and it has been pointed out that it affects the expression levels of the *CXCL5* chemokine (Zineh, 2006). Possible effects of *CXCL5* rs352046, (-156, G>C) in diabetes, cardiovascular diseases, cancer, Behçet's disease have been investigated (Zineh, 2008; Beitelshees, 2012; Arıkan, 2021) and rs352046 was reported as an important marker in the pathogenesis of obesity (Ranjbar, 2008).

In this study, we aimed to understand the *IL-6* (rs2069827, rs1800797, rs1800796, rs1800795), its receptor (*IL-6R*) (rs4845617, rs2228145) and chemokine *CXCL5* (rs352046) polymorphisms possible contributing effects and the relationship of haplotypes and the development of obesity.

Material and methods

Patients and controls

Our study included 60 obesity patients (13 male and 47 female) who were diagnosed according to the international criterias determined by World Health Organization (WHO) (Table 1) and were followed in the Kerolight Healthy Nutrition and Diet Counseling Center, Çivril, Denizli. Obesity patients and 59 healthy controls (HCs) (18 males and 41 females) were selected by calculating body mass index (BMI) and body composition measurements were taken by Tanita Brand MC-580 model scale using Bioelectrical Impedance Analysis (BIA) technology. The data are similar in obese and HCs comparison due to the fact that the female and young individual numbers were high and the age distribution between two groups was similar. In our study, because the sample numbers in other groups were insufficient for statistical calculations, we only examined male and female.

Genotyping

All patients and healthy controls have signed written informed consent after receiving study information. This study was approved by the Ethics Committee of Pamukkale University, Denizli, Turkey (Ethical Approval No: 02.07.2019/12, Denizli/Turkey).
DNA purification and PCR reactions were performed as previously reported (Table 2) (Ranjbar, 2008; Zhang, 2014; Dosseva-Panova, 2015; Ghavimi, 2016; Atalay, 2016).

Statistical analysis

All statistical analyzes were performed according to our previous studies (Atalay, 2016; Arıkan 2021). Data were analyzed to evaluate Hardy-Weinberg equilibrium (HWE), haplotype frequencies and global test of differentiation using Arlequin ver 3.5.1.3 software (Excoffier, 2005).

Table 1. Clinical features of obese and control individuals

Clinical Features		Obese (%)	Control (%)
Sex			
Male		13 (22)	18 (31)
Female		47 (78)	41 (69)
Age	**Range (year)**		
Child	0-17	2 (3)	8 (14)
Youth/middle-age	18-65	55 (92)	50 (85)
Adult /senior	66-79	3 (5)	1 (1)
BMI	**Range (kg/m^2)**		
Underweight	<18.50	-	3 (5)
Normal	18.50-24.99	-	56 (95)
Pre-Obesity (Overweight)	25.00-29.99	28 (47)	-
Class I	30.00-34.99	22 (37)	-
Class II	35.00-39.99	7 (11)	-
Class III (Morbid Obesity)	> 40.00	3 (5)	-

Table 2. Primers and restriction enzymes used in PCR-RFLP

		Primer sequence	PCR product	Restriction enzymes	RFLP results
IL-6	-1363 rs2069827 (G/T)	F: 5′-CgggTCCTgAAATgTTAT-3′ R: 5′- gTTgTCCCTCCAgTCTCC -3′	222 bp	Taq I	G:156+66 bp T:222 bp
	-597 rs1800797 (G/A)	F: 5'-GGAGTCACACACTCCACCT-3' R: 5'-CTGATTGGAAACCTTATTAAG-3'	525 bp	Fok I (BseGI)	G:525bp A:468+57 bp
	-572 rs1800796 (G/C)	F: 5′-CTCCTCTAAgTgggCTgAAg-3' R: 5′-CAAgCCTgggATTATgAAgA-3′	212 bp	Bsrb I (Mb II)	G:139+73 bp C:212 bp
	-174 rs1800795 (G/C)	F: 5'-TgACTTCAgCTTTACTCTTTg-3' R: 5'-CTgATTggAAACCTTATTAAg-3'	198 bp	Nla III (HN1 II)	GG=30+168 bp GC=30+49+168+119 bp CC=49+119 bp
IL-6R	-183 rs4845617 (G/A)	F: 5′-CCATCCgCTCCggCTTTCgTAACC-3′ R: 5′-CgCAggAgCCCggCTCTCTACACA-3′	219 bp	Bcn I (NcII)	G:143+65+11 bp A:208+11 bp
	+48892 rs2228145 (A/C)	F: 5′-gTTAAgCTTgTCAAATggCCTgTT-3′ R: 5′-CAgAggAgCgTTCCgAAgg-3′	258 bp	Hinf I	A:258 bp C:188+70 bp
CXCL5	-156 rs352046 (G/C)	F: 5'-CTCCTCCTggCCACCCTCgC-3' R: 5'-TCAAgCTTTgggATgCTgggggA-3'	114 bp	Nru I (Bsp68 I)	GG=19+95 bp GC=19+95+114 bp CC=114 bp

Results and Discussion

It is known that cytokines are effective not only in the immune system but also in metabolism. It is effective in many metabolic pathways such as glucose and lipid metabolisms, glucose tolerance, insulin resistance, oxidation, lipolysis, triglyceride synthesis, as well as regulation of cell proliferation and apoptosis, especially in liver and adipose tissue (Chen, 2019; Shi, 2019).

It has been shown that insulin resistance changes due to proinflammatory macrophage accumulation and *IL-6* release in adipose tissue in obesity (Bastard 2000). High levels of *CXCL5* also inhibit the insulin-dependent glucose transport in muscle cells and increase the insulin resistance in obese patients (Chavey, 2009a; Chavey, 2009b).This study is one of the first studies to describe the relationship between obesity and possible haplotypes formed by *IL-6* and *IL-6R* gene polymorphisms. When SNP and allele frequencies were observed in obese patients and HCs, we found that *IL-6* SNP rs1800796 and *IL-6R* SNP rs4845617 and rs2228145 frequencies were not consistent with HWE in HCs ($p<0.05$). *IL-6*, rs2069827, rs1800797 and rs1800795 genotype frequencies were consistent with HWE in both groups. Although *CXCL5* rs352046 frequency was consistent with HWE in the obese group, it was not consistent with HWE in the HCs (data not shown). PCR-RFLP results were evaluated with the frequencies of allele and genotype frequencies. It was determined that the genotype and allele frequencies of *IL-6*, rs2069827, rs1800797, *IL-6R*, rs2228145 and *CXCL5*, rs352046 were not statistically different between obese and HCs groups but we found difference in polymorphisms shown in Table 3. A study with adiposity and its long-term changes, Qi et al determined that 5' promoter polymorphism locus; rs2069827 was associated with higher early-adulthood BMI and waist circumference in male and female patients (Qi, 2007). Unlike our results, Tala et al showed that GG genotype of rs1800797 polymorphism significant in *IL-6* levels in diabetic patients (Tala, 2021). In a meta-analysis with obesity, it was emphasized that minor alleles of rs1800795 (C allele) and rs1800797 (A allele) may decrease the risk of obesity but rs1800796 polymorphic region was not associated with obesity (Gholami, 2019). Hsieh et al. reported that the *IL-6R*, rs2228145 region, which we found not to be associated with obesity in our study, is important in modulating *IL-6* level and that there may be a gene-sex relationship with metabolic syndrome (Hsieh, 2012).

Table 3. Genotype and allele frequencies of IL-6 and IL-6R gene polymorphisms in patients with obesity and HCs

		Obese n = 60 (%)	HCs n = 59 (%)	OR (95% Cl)*	P[a]	P[c]
IL-6	rs1800796 (-572, G/C)					
	CC	2 (3.3)	1 (1.7)	2.0000 (0.1764-22.6709)	0.5758	ns
	CG	24 (40)	48 (81.3)	0.1528 (0.0663-0.3519)	< 0.0001	<0.0003
	GG	34 (56.7)	10 (17)	6.4077 (2.7375-14.9988)	< 0.0001	<0.0003
	C-	28 (23.3)	50 (42.4)	0.4139 (0.2367-0.7238)	0.0020	0.004
	G+	92 (76.7)	68 (57.6)	2.4160 (1.3816-4.2246)	0.0020	0.004
	rs1800795 (-174, G/C)					
	CC	0 (0)	0 (0)	0.9835 (0.0192-50.3820)	0.9934	ns
	CG	7 (11.7)	16 (27.1)	0.3550 (0.1339-0.9411)	0.0373	ns
	GG	53 (88.3)	43 (72.9)	2.8173 (1.0626-7.4694)	0.0373	ns
	C+	7 (5.8)	16 (13.6)	0.3949 (0.1562-0.9986)	0.0496	ns
	G-	113 (94.2)	102 (86.4)	2.5322 (1.0014-6.4029)	0.0496	ns
IL-6R	rs4845617 (-183, G/A)					
	AA	11 (18.3)	2 (3.4)	6.3980 (1.3521-30.2735)	0.0193	ns
	AG	36 (60)	50 (84.7)	0.2700 (0.1122-0.6495)	0.0035	0.0105
	GG	13 (21.7)	7 (11.9)	2.0547 (0.7559-5.5851)	0.1581	ns
	A-	35 (29.2)	54 (45.8)	0.4880 (0.2858-0.8332)	0.0086	0.0172
	G+	85 (70.8)	64 (54.2)	2.0491 (1.2002-3.4984)	0.0086	0.0172

OR: Odds ratio, 95% Cl: 95 % confidence interval, where zeros cause problems with computation of the odds ratio or its standard error, 0.5 is added to all cells. P[a]: Statistically significant difference between patients with obesity and HCs ($P < 0.05$), P[c] : Bonferroni correction, ns: not statistically significant.

In our study, *IL-6*, rs1800796 GG genotype and *IL-6R*, rs4845617 AG genotype frequencies were found higher and statistically significant between obese and HCs. Boeta-Lopez et al studied anti-inflammatory, anti-obesity and glucose homeostatic roles of *IL-6* polymorphisms and showed a relation between C allele of rs1800796 with obesity but not with rs1800797 (Boeta-Lopez, 2017). Although no association of rs1800795 and rs1800796 was found in colorectal cancer for which obesity is a risk factor, a study suggests that *IL-6* polymorphisms are significant in severely affected patients but not in low-grade obesity (Maculewicz, 2021). Similar to our study, Bustamante et al emphasized the importance of *IL-6R* SNPs and showed that *IL-6R*, rs4845617, GG genotype was associated with increase of BMI and obesity in females (Bustamante, 2007).

We determined that *IL-6*, rs1800795, GG and CG genotypes, C and G alleles were found statistically significant between obese and HCs. Our results suggest that GG genotype and G allele may be risk factors for obesity. However, the statistical significance of rs1800795 genotypes and alleles were lost when Bonferroni correction is applied (Table 3). Some studies have found that the *IL-6*, rs1800795 C allele increases the risk of obesity and overweight, and the obesity risk effect is approximately similar in different ages (Hu, 2018; Gholami, 2019). Also, Möhlig et al claimed that increasing BMI was correlated with higher *IL-6* concentrations for the CC genotype than for GG the genotype of rs1800795 and obesity is more deleterious for patients carrying the CC genotype than for those with the GG genotype (Möhlig, 2004).

Although *CXCL5* gene polymorphisms are accepted as an important marker, rs352046 locus was not found to be associated with obesity in our study (data not shown). Since it is thought to be effective in the development of various diseases and obesity (Amoli, 2005; Chavey, 2009a), researchers emphasize the investigation of different loci of *CXCL5* in obesity (Kitahara, 2014).

Since the number of female individuals was higher in the obese and HCs groups than the males, a statistically significant difference was found between the obese female and healthy female groups in *IL-6* (rs1800796, rs1800795) and *IL-6R* (rs4845617) alleles and genotypes. When the genotype and allele frequencies of *IL-6*, *IL-6R* and *CXCL5* SNPs in male obese and male HCs groups were compared, no statistically significant difference was observed. Furthermore, there was no statistically significant difference in between obese and HCs female individuals in *CXCL5*, rs352046.

other in frequency and number were determined by using with *IL-6* SNPs in obese and HCs and four Nine haplotypes, different from each haplotype were determined with *IL-6R* SNPs (Table 4). Interestingly, according to OR calculations, only the GGCG haplotype (p=0.0091) probable frequency distribution was found to be different in obese and normal healthy individuals. Other haplotype studies with *IL-6* polymorphic regions have had conflicting results about functional haplotypes or polymorphisms associated with obesity or diabetes (Qi 2007; Ng 2008).

When *IL-6/IL-6R* haplotypes together were examined with OR calculations in our study, we observed that the GGGGGC haplotype was a higher in both group but there was no statistically significant difference between obese patients and HCs (p=1.000). However, haplotype GGGGAA is significantly different between obese and HCs (p=0.0018) (Table 5). Our results suggest that polymorphisms and haplotypes in cytokines have a wide diversity and importance in obese patients.

Table 4. Haplotypes and frequencies of IL-6 and IL-6R in patients with obesity and HCs

	Haplotypes	Obese (% ± sd)	HCs (% ± sd)	OR	95% Cl	P	P[c]
			IL-6				
1	GGGG	61.67 ± 4.46	37.29 ± 4.47	1.63	0.96- 2.78	0.0723	ns
2	GGCG	20.83 ± 3.72	38.14 ± 4.49	0.43	0.23 – 0.81	0.0091	ns
3	GAGG	6.67 ± 2.29	5.09 ± 2.03	1.43	0.44 – 4.67	0.5533	ns
4	GAGC	5.83 ± 2.15	11.02 ± 2.89	0.52	0.18 – 1.45	0.2113	ns
5	TGGG	1.67 ± 1.17	0.85 ± 0.85	3.06	0.31 – 29.95	0.3362	ns
6	TGCG	1.67 ± 1.17	4.24 ± 1.86	0.49	0.08 – 2.74	0.4162	ns
7	TAGG	0.83 ± 0.83	-	3.03	0.12 – 75.28	0.4988	ns
8	GACG	0.83 ± 0.83	-	3.03	0.12 – 75.28	0.4988	ns
9	GGGC	-	3.39 ± 1.67	0.14	0.01 – 2.72	0.1931	ns
			IL-6R				
1	GC	35.00±4.37	43.22±4.58	0.71	0.40 – 1.27	0.2468	ns
2	AA	28.33±4.13	35.59±4.43	0.69	0.38 – 1.26	0.2262	ns
3	AC	20.83±3.72	10.17±2.79	2.39	1.06 – 5.39	0.0351	ns
4	GA	15.83±3.35	11.02±2.90	1.54	0.68 – 3.51	0.3033	ns

Table 5. Haplotypes and frequencies of *IL-6* and *IL-6R* together in patients with obesity and HCs

	Haplotypes	Obese (% ± sd)	HCs (% ± sd)	OR	95% Cl	P	P[c]
			IL-6 / IL-6R				
1	GGGGGC	25.83 ± 4.01	26.27 ± 4.07	1.00	0.53 -1.89	1.0000	ns
2	GGGGAA	17.50 ± 3.48	2.54 ± 1.46	10.76	2.42- 47.73	0.0018	0.034
3	GGGGGA	9.17 ± 2.65	5.08 ± 2.03	1.88	0.61 – 5.82	0.2741	ns
4	GGGGAC	9.17 ± 2.65	3.39 ± 1.67	3.2	0.84 – 12.18	0.0885	ns
5	GGCGAC	7.50 ± 2.41	6.78 ± 2.32	1.16	0.40 – 3.32	0.7885	ns
6	GGCGAA	6.67 ± 2.29	27.97 ± 4.15	0.19	0.08 – 0.47	0.0003	0.005
7	GGCGGA	5.00 ± 1.80	2.54 ± 1.46	2.58	0.49 – 13.62	0.2645	ns
8	GAGCGC	4.17 ± 1.83	8.48 ± 2.58	0.42	0.12 – 1.42	0.1622	ns
9	GAGGGC	3.33 ± 1.655	4.24 ± 1.86	0.74	0.16 – 3.40	0.7014	ns
10	GAGGAC	2.50 ± 1.43	-	7.22	0.37 – 141.53	0.1931	ns
11	GAGCAA	1.67 ± 1.17	0.85 ± 0.85	2.02	0.18 – 22.64	0.5684	ns
12	GGCGGC	1.67 ± 1.17	0.85 ± 0.85	2.02	0.18 – 22.64	0.5684	ns
13	TGCGGA	0.83 ± 0.83	0.85 ± 0.85	1.00	0.06 – 16.21	1.0000	ns
14	TGGGAC	0.83 ± 0.83	-	3.03	0.12 – 75.28	0.4988	ns
15	TGGGAA	0.83 ± 0.83	0.85 ± 0.85	1.00	0.06 – 16.21	1.0000	ns
16	AGCGAA	0.83 ± 0.83	3.39 ± 1.67	0.33	0.03 – 3.20	0.3362	ns
17	GAGGGA	0.83 ± 0.83	-	0.03	0.12 – 75.28	0.4988	ns
18	TATGAA	0.83 ± 0.83	-	0.03	0.12 – 75.28	0.4988	ns
19	GAGGAC	0.83 ± 0.83		0.03	0.12 – 75.28	0.4988	ns
20	GGGCGC	-	3.39 ± 1.67	1.14	0.01 – 2.72	0.1931	ns
21	GAGCGA	-	1.70 ± 1.19	0.20	0.01 – 4.14	0.2949	ns

Another important result to understand the importance of haplotype data is global test of differentiation and we determined that there was a statistically difference in *IL-6* haplotypes between obese/HCs and female obese/female HCs, no significant difference in *IL-6R* haplotypes. Together with these findings, *IL-6/IL-6R* haplotype results with the global difference test showed a significant difference between obese and HCs, female obese/female HCs and male obese/male HCs ($p<0.05$). These results suggested that *IL-6* and *IL-6R* haplotypes may be in different genetic structure in obese and HCs.

Conclusion

We concluded that the *IL-6* rs1800796, rs1800795 and *IL-6R* rs4845617 G allelles could be the possible genetic factors responsible for obesity. Haplotype structures may differ depending on different populations and also even subgroups of the same population. Our study emphasizes that *IL-6* and *IL-6R* haplotypes are one of the important possible genetic factors in the development of obesity.

Although our results point to several genetic features, larger studies should be conducted for different genetic factors in relation with obesity, which is a multifactorial disease. The limitations of our study are the low number of obese and HCs limited to a small region, and their exposure to the same environmental factors.

In addition, genetic studies should be evaluated according to well-defined clinical features of obesity such as body mass index (BMI), age (adolescent, youth, adult) or other underlying diseases. We also propose to examine other cytokines, cytokine receptors and proteins such as adiponectin, lectin and ghrelin to elucidate genetic differences in obesity.

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Conflict of interest

Authors declare that they have no conflict of interest.

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