Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Influence of IL-10, IL-6 and TNF-α gene polymorphism on obesity

Sarhang Hasan Azeez*

Biology Department, College of Education, Salahaddin University-Erbil, Kurdistan Region-Iraq

ARTICLE INFO

Original paper

Article history:
Received: July 14, 2023
Accepted: November 24, 2023
Published: December 31, 2023

Keywords:

IL-10, IL-6, TNF-α, Polymorphism, Obesity, Inflammatory indicators

ABSTRACT

Obesity is one of the most serious public health issues. Obesity is caused by a complex interaction of genetic, metabolic, social, cultural, and environmental variables. Obesity prevalence in both children and adults has risen substantially in recent years, and the condition is now considered an epidemic. Forty-two obese males with BMI≥ 30 were included in this study. Their age interval was (16-45) years. Controls include 42 males with normal BMI≤25 and age group (16-45) years were selected. Serum level and single nucleotide polymorphism were determined for IL-10, IL-6 and TNF-α. For evaluating gene polymorphism, the allele was counted by direct allele counting. The Hardy–Weinberg equilibrium was assessed with the $\chi 2$-test. In IL-10 the GA genotype was found about 5th folded than controls with (OR:4.71, C.I:1.86 to 11.91). IL-6 genotype GG was revealed as an etiologic factor and GC as a protective factor for obesity. While for TNF-α the GG genotype was protective and GA was a risk factor for obesity. Point mutation in G/A for IL-10 and TNF-α were considered as developing factors, whereas the GG genotype was etiologic to obesity in this study.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.15.46

Introduction

Obesity is one of the most serious public health issues. Obese children had a 20-year reduction in life expectancy if they remained obese into young adulthood (1). North African countries and the Middle East region, like other developing countries, are not immune to global issues (2). Obesity is caused by a complex interaction of genetic, metabolic, social, cultural, and environmental variables. Obesity prevalence in both children and adults has risen substantially in recent years, and the condition is now considered an epidemic. According to the Centers for Disease Control and Prevention, the United States has the highest rate of obesity, estimated at over 40% in 2010. This is comparable to the 38 percent incidence rate observed in Europe, but just 22% in Southeast Asia (1).

The adipose tissue of obese people is characterized by a lower level of inflammation and a higher level of specific cytokines. Seven studies have found a link between tumor necrosis factor (TNF)-a, interleukin (IL)-6, leptin levels, adipose mass, and body mass index (BMI) (3). TNF-a and IL-6 have been discovered to have the worst effects because they interfere with adipose tissue's normal function, impacting adipogenesis and contributing to obesity consequences (4).

Advances in human genome variation have led to the identification of genes that may have a role in obesity and other disorders; nevertheless, few researches have focused particularly on the connections between obesity and genetic polymorphism (5). Interleukin-6 (IL-6) is a pro-inflammatory immune modulator cytokine that regulates the acute phase response (6). Obese patients, as well as those with chronic inflammatory diseases and aberrant blood lipid concentrations, had high IL-6 serum levels. In a state of obesity, adipose tissue has been proven to produce considerably more interleukin-6. Increased IL-6 levels in obese people may lead to insulin resistance and an increased risk of cardiovascular disease (7).

The polymorphisms of IL-6 (especially174G/C) influence plasmatic levels of cytokines and their transcriptional regulation, as shown in many population-based genetic studies that have been conducted to determine whether there is an association between obesity and IL-6 (174G/C) polymorphisms, but the results were inconclusive, with many controversies (8,9).

Obesity, particularly visceral obesity, is also recognized to be an independent risk factor for T2DM development. Adipose tissue, in reality, is an endocrine organ that governs the entire body's metabolism. It may make a range of cytokines (TNF-, IL-6, IL-1), as well as other bioactive substances including leptin, resistin, and monocyte chemoattractant protein-1 (MCP-1/CCL2) (3). Pro-inflammatory immune cells (CD8+ T lymphocytes, IFN-+ Th1 cells, B cells, mast cells, neutrophils, and M1 macrophages) are drawn to obese people's adipose tissue by chemokines produced by stressed adipocytes in response to lipid excess (10).

Single nucleotide polymorphisms (SNPs) in the regulatory regions of genes can influence the production of pro- and anti-inflammatory cytokines (8). Some research has looked into the link between TNF-, IL-6, and IL-10 gene polymorphisms and metabolic disorders (11,12). Despite these studies, there is still a lot of debate over the relevance of inflammatory indicators and SNPs in cytokine genes in the development of diabetes (13).

The etiology of obesity in humans has been linked

* Corresponding author. Email: sarhang.azeez@su.edu.krd

to a number of potential genes. TNF- (tumor necrosis factor) is a cytokine produced predominantly by adipocytes, and high levels of this cytokine have been related to obesity and insulin resistance. The TNF-messenger Human RNA levels are favourably linked with BMI, fat mass, and insulinemia and are inversely correlated with lipoprotein lipase activity in skeletal muscle and adipose tissue (14). On the short arm of chromosome 6, there is a gene that codes for human TNF- α (15). Recently, two nucleotide polymorphisms in the TNF-gene promoter region have gotten a lot of attention: G A replacements at 308 and 238 respectively. TNF- is a key regulator of gene expression that has been linked to both obesity and obesity-related diseases. By reducing lipase activity and boosting de novo fatty acid synthesis in the liver, TNF-a affects lipid metabolism and can lead to hypertriglyceridemia (16). TNF-a 308 G>A increases the expression of this cytokine in adipose tissue, which affects gene expression (a modulator of this gene). Because the A allele of this gene is more common in obese children, it is the gene polymorphism that has received the most attention (17).

Materials and Methods

Forty-two obese males with BMI≥ 30 were included in this study. Their age interval was (16-45) years. Controls include 42 males with normal BMI≤25 and age group (16-45) years were selected. The consent form was confirmed by the participants of the study. Seven milliliters of venous blood was withdrawn from the antecubital vein and collected from each participant. Levels of serum IL-10, IL-6 and TNF-α were determined by enzyme-linked immune sorbent assay (ELISA) and the Cloud Clone Corp kit was used according to the manufacturer's protocol.

Using the manufacturer's instruction for the QLAmp DNA mini kit (Qiagen, Hilden, Germany), peripheral blood mononuclear cells were used to obtain genomic DNA for both patients and control groups. IL-10, IL-6 and TNF-α genotype, the amplification refractory mutational system method (ARMS-PCR) was utilized. The assays were performed in a 20 μL reaction volume containing 40 ng genomic DNA, 1.5 Mm dNTPs, 25Mm MgCl2, 1 μL of 10 pmol each primer and 0.4 units of Tag polymerase (Fermentas, Maryland, USA) in 1 X Reaction Buffer. The primer sequences were as follows: IL -10 generic primer, 5′-CAGTGC-CAACTGAGAATTTGG-3′, IL -10 (G) Allele Primer 5′-CTACTAAGGCTTCTTTGG-GAG- 3, and IL -10 (A) Allele Primer 5′-ACTACTA-AG-GCTTCTTTGGGAA-3. The PCR reaction was carried out in a thermal cycler (PX2) with the following cycling conditions: 95°C for 3 minutes, followed by 35 cycles at 95°C for 45 seconds, 58°C for 40 seconds, 72°C for 1 minute, and finally a 7-minute extension at 72°C. The primer sequences were as follows: IL -6 generic primer, 5′-GCCTCAGAGACATCACCAGTC C-3′, IL -6 (G) Allele Primer 5′-CCCCTAGTTGTGTCTTGC G-3′, and IL -6 (C) Allele Primer 5′-CCCCTAGTTGTGTCTTGCC-3′. Cycling conditions were as follows: 1 minute at 95ºC, followed by 10 cycles of 15 seconds at 95°C, 50 seconds at 58°C, 40 seconds at 72 ℃, followed by 20 cycles of 20 seconds at 95 ℃, 50 seconds at 54°C and 50 seconds at 72°C, with 5 minutes at 72 ℃ as the final extension. For TNF-α common primer 5'-TCC TCCCTGCTC-CGATTCCG-3'; TNF-α (A) Allele Primer 5'-CAA-TAAGTTTTG AGGGGCATGA-3'; TNF-α (G) Allele Primer 5'-CAATAAGTTTTGAGGGGC ATG G-3' with cycling conditions: 95 C for 2 minutes, followed by 35 cycles at 95 C for 45 seconds, 58 C for 40 seconds, 72 C for 1 min, and finally a 7 minutes extension at 72 C. The amplicon size for IL-10 was 258bp, IL-6 was 230bp and for TNF-α was 104bp. The amplified products were analyzed on 2% agarose gel.

All statistical analyses were performed using an SPSS 19.0 (SPSS Inc., Chicago, IL, USA) statistical package. Normally distributed variables were expressed as mean ± SD as appropriate. A P value<0.05 was considered to be statistically significant. Between-group comparisons were assessed for categorical variables with the (ANOVA) test was used for the variables and serum cytokine concentration.

For IL-10, IL-6 and TNF-α gene polymorphism, the allele was counted by direct allele counting. The Hardy–Weinberg equilibrium was assessed with the χ2-test. Descriptive data are presented as means ± standard deviations (SDs). Genotype and allele frequencies were compared between groups using a χ2-test of independence with 2x2 contingency tables and the z statistics. Statistical significance of the variables was established at the level P<0.05.

Results

Results of the present study showed that the serum level of the studied cytokines IL-10 and IL-6 were significantly increase in the obese participants in comparison to control, p<0.05. Whereas the TNF- α level was dropped no significantly (p=0.96, Table 1).

Regarding the IL-10-1082GA gene polymorphism the results revealed that the GG genotype carriers were less in obese than control, the OR: 0.19, (C.I:0.07-0.51), and this genotype was protective against obesity. The GA genotype was found more than 4-folded in obese than control with the OR: 4.71, (C.I: 1.86-11.91) and the carrier were considered as risk factor to obesity. The AA genotype was found exact recordings in obese and control, and there was no effect for this genotype on obesity. About the allele carriers, the *G* allele showed to be protective for the obesity and the *A* allele was thought to be a risk factor for being obese (Tables 2 and 3).

The IL-6-174GC gene polymorphism the findings were revealed that GG was found increased 2- folded in obese

Table 1. Serum level of IL-10, IL-6, TNF-α, obese and controls.

Cytokine	Cytokine Serum Mean Level ± S.D. (pg/ml)		P value
	Obese (No. = 42)	Control (No. = 42)	
IL-10	30.73±5.5	5.7±0.85	0.001
IL-6	35±4.75	2.02±0.56	0.0001
TNF-α	2.12±0.61	5.6±0.59	0.96

significantly, the OR: 2.91, C.I: (1.16-7.31), and it was remarkably risk factor for obesity. The GC producers were decreased significantly in obese individuals compared to control, OR: 0.22, (C.I: 0.08-0.63), hence, this genotype has protective effect on obesity. Genotype CC carriers were increased in obese and there was double folded risk to get obesity, OR: 2.11, (C.I: 0.37-11.92). Allele frequency for this genotype showed that the *G* allele was risky for being obese for male and the *C* allele was considered as protective against the obesity (Tables 4 and 5).

Results of the present study for TNF-α-308GA polymorphism were the GG genotype was decreased significantly in obese male, the OR: 0.15, (C.I: 0.06-0.40). However, this genotype was protective to obesity in male. The GA genotype carriers were found increased more than 6-folded in obese participants, OR: 6.4, (C.I: 2.49-16.47), and it was risk factor for obesity. Moreover, the AA genotypes were found similar in both groups of the participants, and this genotype has no effect on obesity according to the results of our study. So presence of *G* allele was protective against obesity and *A* allele was at risk to obesity (Tables 6 and 7).

Discussion

Based on experimental data on mice, several scientists studied the relationship between polymorphisms in the IL-6 gene and obesity and found that they had an impact on fat mass, fat metabolism, and body mass, as well as the development of obesity (8). Yu et al. (18) discovered that the IL-6 (174 G/C) polymorphism was similarly linked to obesity after reviewing 48 research with results comparable to ours.

The identified C allele in both C/C homozygotes and G/C heterozygotes of the IL6 (174 G/C) gene was linked to a substantial increase in the total of 10 skinfold thickness measures in obese girls in research by Popko et al. (19). The G allele at C-174 was shown to be more prevalent in lean people by Ibrahim et al (8), whereas the C allele was found to be linked with obesity indices. These findings contradict the findings of our study, which found that in the obese group, the GC heterozygote genotype predominated and the GG genotype was less prominent than in the healthy weight group. This is due to the fact that it was a pilot research with a limited sample size.

Table 2. Observed numbers and percentage frequencies and (H-W) equilibrium of IL10-1082 genotypes and alleles in obese and controls.

Groups			*IL10*-$_{1082}$ Genotype or Allele					H-W P ≤
			GG	GA	AA	*G*	*A*	
Obese (N=42)	Observed	No.	8	32	2	48	36	Significant
		%						
	Expected	No.	13.7	20.6	7.7	Not Estimated		
		%						
Controls (N=42)	Observed	No.	23	17	2	63	21	Not significant
		%						
	Expected	No.	23.6	15.8	2.6	Not Estimated		
		%						

Table 3. Statistical evaluations of associations between IL10-1082 genotypes or alleles and obese.

IL10-$_{1082}$ Genotype or Allele	Statistical Evaluations			
	Relative Risk	Etiological Or Preventive Fraction	Fisher's Exact Probability	95% Confidence Intervals
GG	0.19	0.44	Significant	0.07 to 0.51
GA	4.71	0.6	Significant	1.86 to 11.91
AA	1	ref	Non-Significant	0.14 to 7.27
G	0.44	0.42	Significant	0.23 to 0.85
A	2.1	0.24	Significant	1.17 to 4.32

Table 4. Observed numbers and percentage frequencies and H-W equilibrium of IL6-174 genotypes and alleles in obese and controls.

Groups			*IL6*-$_{174}$ Genotype or Allele					H-W P ≤
			GG	GC	CC	*G*	*C*	
Obese (N=42)	Observed	No.	32	6	4	70	14	Significant
		%						
	Expected	No.	29.15	11.7	1.15	Not Estimated		
		%						
Controls (N=42)	Observed	No.	22	18	2	62	22	Not significant
		%						
	Expected	No.	22.9	16.2	2.9	Not Estimated		
		%						

Table 5. Statistical evaluations of associations between IL6-174 genotypes or alleles and obese.

IL6-$_{174}$ Genotype or Allele	Statistical Evaluations			
	Relative Risk	**Etiological or Preventive Fraction**	**Fisher's Exact Probability**	**95% Confidence Intervals**
GG	2.91	0.5	Significant	1.16 to 7.31
GC	0.22	0.33	Significant	0.08 to 0.63
CC	2.11	0.05	Non-Significant	0.37 to 11.92
G	1.77	0.36	Non-Significant	0.84 to 3.75
C	0.56	0.11	Non-Significant	0.27 to 1.19

Table 6. Observed numbers and percentage frequencies and H-W equilibrium of TNF-α-308 genotypes and alleles in obese and controls.

Groups			*TNF-α* $_{-308}$**Genotype or Allele**					**H-W P ≤**
			GG	**GA**	**AA**	***G***	***A***	
Obese (N=42)	Observed	No.	9	32	1	50	34	Significance
		%						
	Expected	No.	14.9	20.2	6.9	Not Estimated		
		%						
Controls (N=42)	Observed	No.	27	14	1	68	16	Not significance
		%						
	Expected	No.	27.5	13	1.5	Not Estimated		
		%						

Table 7. Statistical evaluations of associations between TNF-α-308 genotypes or alleles and obese.

TNF-α$_{-308}$ Genotype or Allele	Statistical Evaluations			
	Relative Risk	**Etiological or Preventive Fraction**	**Fisher's Exact Probability**	**95% Confidence Intervals**
GG	0.15	0.54	Significant	0.06 to 0.40
GA	6.4	0.64	Significant	2.49 to 16.47
AA	1	ref	Non-Significant	0.06 to 15.99
G	0.35	0.53	Significant	0.17 to 0.69
A	2.89	0.27	Significant	1.44 to 5.78

Saxena et al. (12) earlier observed that the CC genotype was extremely uncommon in their research. Similarly, to our findings, an Iranian research of 242 people found that obese people had more G alleles, but the difference was statistically insignificant (20). Another meta-analysis found no significant correlations between IL6 (174G/C) genotypes and waist-to-hip ratio, waist circumference, or central obesity, indicating that this polymorphism may not play a role in obesity (21).

Carriers of the C allele for the IL-6 polymorphism G174C have a higher BMI, according to a study. Because the G174C gene polymorphism is thought to impact IL-6 production and physiological control, it may also affect obesity and insulin sensitivity (8).

The significance of TNF-, IL-6, and IL-10 levels in obesity, as well as their relationship with gene polymorphisms, was investigated in this study. IL-10 is an anti-inflammatory cytokine that regulates the immune system by decreasing cytokine production, tissue factor expression, matrix-degrading metalloproteinase inhibition, and lymphocyte phenotypic flipping to the Th2 phenotype (22). T-cells, B-cells, monocytes, and macrophages all generate this cytokine, and 75 percent of the variance in IL-10 production is thought to be hereditary (23). An important research found that IL-10 levels were lower in people with impaired glucose tolerance or T2DM compared to people with normal glucose tolerance and that IL-10 levels were inversely related to BMI (24).

BMI, waist circumference, hs-CRP, and IL-10 levels were all positively associated with IL-6 levels. hs-CRP, on the other hand, revealed a substantial positive association. BMI, waist circumference, hs-CRP, and IL-10 levels were all positively associated with IL-6 levels. hs-CRP, on the other hand, revealed a substantial positive association (25).

The TNF-a 308 G>A gene polymorphism is a key regulator of metabolism and has been linked to metabolic problems in both adults and children. Although there have been several genetic research on the TNF-a 308 G>A gene polymorphism in adult populations, only a few have focused on metabolic diseases and only a few of them have highlighted the possible significance of the TNF-a gene in metabolic syndrome (26). The role of the TNF-a 308 G>A gene polymorphism on obesity and inflammatory state is

little understood. 10 Obesity is generally known to be an inflammatory disease, but TNF-a has also been linked to other inflammatory disorders in children, including gastritis (27). Nonetheless, numerous TNF-a gene polymorphisms, including TNF-a 308 G>A and TNF-a 238 G>A, have been linked to nutritional problems in children and adults. Only the TNF-a 308 G>A gene polymorphism has been linked to obesity among these gene polymorphisms. As a result of the foregoing findings, the current research focuses on the TNF-a 308 G>A gene polymorphism (28). One study (16), which looked at the association between TNF-a levels and patient age and BMI, found that the G/G genotype was linked to increased TNF-a levels in men of normal weight, but had no impact in men with a BMI of more than 25 kg/m2. In terms of age, the same research found a steady decline in TNF-a levels between the ages of 5 and 17,8, but Arican et al. (29) in 2005 found a rise in TNF-a levels in the 5e10 year age group, followed by a drop in the 10e15 year age group.

In addition to TNF-a, El-Mikkawy et al (30) investigated the connection between IL-6 secretion and obesity, concluding that obese patients had insufficient IL-6 secretion. Because of the small number of patients included in the study, there was no significant difference in age or gender between the control and overweight groups in this study; nevertheless, our major objective is to expand our inquiry in the future. Dalziel et al. (31) also discovered that obese TNF-a 308 A allele carriers exhibited a net relationship between insulin resistance and HDL cholesterol, indicating that dyslipidemia plays a larger role in the development of insulin resistance in these individuals. The current study, however, showed no statistically significant relationship between the TNF-a 308G>A gene polymorphism and any of the biochemical variables investigated ($p > 0.05$). Chang et al. also found that the TNF-a-308 G>A gene polymorphism was linked to obesity (32), but Włodarczyk et al. (33) found that the AA and GA genotypes of TNF-a 308 G>A were linked to a greater risk of obesity in men, but only the AG genotype was linked to a higher risk of obesity in women. The AA and GA homozygotes were also shown to have an increased risk of developing obesity-related metabolic disorders (34). Hedayati, on the other hand, found no link between the TNF-a 308 G>A gene polymorphism and obesity in an Iranian population (16). Women with the variant genotype of the TNF-a 308 G>A gene polymorphism who had poor adherence to the Mediterranean diet had a 3.5-fold increased risk of becoming overweight/ obese, according to Barchitta et al. (35), similar to those with a low socioeconomic status who also had a higher risk of obesity. Brand et al., on the other hand, postulated that the G-308 G>A polymorphism of the TNF-a gene was linked to BMI, therefore serving as a genetic marker for greater obesity susceptibility in the Caucasian population (36).

The above discussion demonstrates that the literature's evidence on the link between the TNF-a 308 G>A gene polymorphism and obesity is inconsistent. Other evidence has also been found that supports a significant negative association between A-allele carriers and BMI (31), a result supported by the current finding that the variant genotype (GA or AA) of the TNF-a 308 G>A gene polymorphism was more common among normal-weight children than overweight children. As a result, genotypes of the TNF-a 308 G>A gene polymorphism have been shown to play a role in the likelihood of becoming overweight or obese in people (32). However, further research is needed to determine if these variant genotypes have a detrimental or beneficial influence, as well as to pinpoint the mechanism behind such an effect. The majority of research claims that these genotypes increase the chance of becoming obese; nevertheless, there are contradicting findings in the literature, which, like the current findings, emphasize the detrimental influence of these genotypes on weight status.

Acknowledgments
None.

Interest conflict
The author declares that he has no conflict of interest.

Author's contribution
Sarhang Hasan Azeez did all the work alone.

References

1. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. Pharmacoeconomics 2015;33:673–89.
2. Nishida C, Barba C, Cavalli-Sforza T, Cutter J, Deurenberg P, Darnton-Hill I, et al. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
3. Makki K, Froguel P, Wolowczuk I. Adipose Tissue in Obesity-Related Inflammation and Insulin Resistance: Cells, Cytokines, and Chemokines. ISRN Inflamm 2013;2013:1–12.
4. Cawthorn WP, Sethi JK. TNF-α and adipocyte biology. FEBS Lett 2008;582:117–31.
5. Qi L, Cho YA. Gene-environment interaction and obesity. Nutr Rev 2008;66:684–94.
6. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014;6:a016295.
7. Kern L, Mittenbühler MJ, Vesting AJ, Ostermann AL, Wunderlich CM, Wunderlich FT. Obesity-induced TNFα and IL-6 signaling: The missing link between obesity and inflammation- driven liver and colorectal cancers. Cancers (Basel) 2019;11:24.
8. Ibrahim OM, Gabre AA, Sallam SF, El-Alameey IR, Sabry RN, Galal EM, et al. Influence of Interleukin-6 (174G/C) gene polymorphism on obesity in egyptian children. Open Access Maced J Med Sci 2017;5:831–5.
9. Hu M, Yu Z, Luo D, Zhang H, Li J, Liang F, et al. Association between -174G>C polymorphism in the IL-6 promoter region and the risk of obesity A meta-analysis. Med (United States) 2018;97.
10. Xu L, Kitade H, Ni Y, Ota T. Roles of chemokines and chemokine receptors in obesity-associated insulin resistance and nonalcoholic fatty liver disease. Biomolecules 2015;5:1563–79.
11. Haddy N, Sass C, Maumus S, Marie B, Droesch S, Siest G, et al. Biological variations, genetic polymorphisms and familial resemblance of TNF-α and IL-6 concentrations: STANISLAS cohort. Eur J Hum Genet 2005;13:109–17.
12. Saxena M, Srivastava N, Banerjee M. Association of IL-6, TNF-α and IL-10 gene polymorphisms with type 2 diabetes mellitus. Mol Biol Rep 2013;40:6271–9.
13. Banerjee M. Genetic polymorphisms of cytokine genes in type 2 diabetes mellitus. World J Diabetes 2014;5:493.
14. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409–15.
15. El-Tahan RR, Ghoneim AM, El-Mashad N. TNF-α gene polymor-

phisms and expression. Springerplus 2016;5:1–7.
16. Hedayati M, Sharifi K, Rostami F, Daneshpour MS, Zarif Yeganeh M, Azizi F. Association between TNF-α promoter G-308A and G-238A polymorphisms and obesity. Mol Biol Rep 2012;39:825–9.
17. Banday MZ, Balkhi HM, Hamid Z, Sameer AS, Chowdri NA, Haq E. Tumor necrosis factor-α (TNF-α)-308G/A promoter polymorphism in colorectal cancer in ethnic Kashmiri population - A case control study in a detailed perspective. Meta Gene 2016;9:128–36.
18. Yu Z, Han S, Cao X, Zhu C, Wang X, Guo X. Genetic polymorphisms in adipokine genes and the risk of obesity: A systematic review and meta-analysis. Obesity 2012;20:396–406.
19. Popko J, Karpińnski M, Chojnowska S, Maresz K, Milewski R, Badmaev V, et al. Decreased levels of circulating carboxylated osteocalcin in children with low energy fractures: A pilot study. Nutrients 2018;10:734.
20. Kalantari N, Doaei S, Keshavarz-Mohammadi N, Gholamalizadeh M, Pazan N. Review of studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions. ARYA Atheroscler 2016;12:281–90.
21. Qi L, Zhang C, Van Dam RM, Hu FB. Interleukin-6 genetic variability and adiposity: Associations in two prospective cohorts and systematic review in 26,944 individuals. J Clin Endocrinol Metab 2007;92:3618–25.
22. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci 2019;20:6008.
23. Rojas JM, Avia M, Martín V, Sevilla N. IL-10: A multifunctional cytokine in viral infections. J Immunol Res 2017;2017.
24. Rodrigues KF, Pietrani NT, Bosco AA, Campos FMF, Sandrim VC, Gomes KB. IL-6, TNF-α, and IL-10 levels/ polymorphisms and their association with type 2 diabetes mellitus and obesity in Brazilian individuals. Arch Endocrinol Metab 2017;61:438–46.
25. Marques-Vidal P, Bochud M, Bastardot F, Lüscher T, Ferrero F, Gaspoz JM, et al. Association between inflammatory and obesity markers in a swiss population-based sample (CoLaus Study). Obes Facts 2012;5:734–44.
26. Gupta V, Gupta A, Jafar T, Gupta V, Agrawal S, Srivastava N, et al. Association of TNF-α promoter gene G-308A polymorphism with metabolic syndrome, insulin resistance, serum TNF-α and leptin levels in Indian adult women. Cytokine 2012;57:32–6.
27. Golshani H, Haghani K, Dousti M, Bakhtiyari S. Association of TNF-α 308G/A polymorphism with type 2 diabetes: A case-control study in the Iranian Kurdish ethnic group. Osong Public Heal Res Perspect 2015;6:94–9.
28. Jamil K, Jayaraman A, Ahmad J, Joshi S, Yerra SK. TNF-alpha −308G/A and −238G/A polymorphisms and its protein network associated with type 2 diabetes mellitus. Saudi J Biol Sci 2017;24:1195–203.
29. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005;2005:273–9.
30. El-Mikkawy DME, EL-Sadek MA, EL-Badawy MA, Samaha D. Circulating level of interleukin-6 in relation to body mass indices and lipid profile in Egyptian adults with overweight and obesity. Egypt Rheumatol Rehabil 2020;47:1–7.
31. Dalziel B, Gosby AK, Richman RM, Bryson JM, Caterson ID. Association of the TNF-α -308 G/A promoter polymorphism with insulin resistance in obesity. Obes Res 2002;10:401–7.
32. Yang YH, Liu YQ, Zhang L, Li H, Li X Bin, Ouyang Q, et al. Genetic polymorphisms of the TNF-α-308G/A are associated with metabolic syndrome in asthmatic patients from Hebei province, China. Int J Clin Exp Pathol 2015;8:13739–46.
33. Włodarczyk M, Ciebiera M, Nowicka G. TNF-α G-308A genetic variants, serum CRP-hs concentration and DNA damage in obese women. Mol Biol Rep 2020;47:855–66.
34. Leońska-Duniec A, Ficek K, Świtała K, Cięszczyk P. Association of the TNF-α -308G/A polymorphism with lipid profile changes in response to aerobic training program. Biol Sport 2019;36:291–6.
35. Barchitta M, Quattrocchi A, Adornetto V, Marchese AE, Agodi A. Tumor necrosis factor-alpha -308 G>A polymorphism, adherence to mediterranean diet, and risk of overweight/obesity in young women. Biomed Res Int 2014;2014.
36. Brand E, Schorr U, Kunz I, Kertmen E, Ringel J, Distler A, et al. Tumor necrosis factor-α -308 G/A polymorphism in obese Caucasians. Int J Obes 2001;25:581–5.