ORIGINAL ARTICLE

Association of -174 G>C interleukin-6 gene polymorphism with interleukin-6 and c-reactive protein levels and obesity: A case–control study among people/residents of Western Indonesia

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ABSTRACT

Background: Interleukin-6 (IL-6) and C-Reactive Protein (CRP) are mediators of inflammatory responses and increase in people who are obese . The increase of IL-6 and CRP levels is modified by polymorphism of -174 G>C IL-6 gene.

Aim: The purpose of this study was to investigate the relationship between -174 G>C IL-6 polymorphism gene on the level of IL-6 and CRP in the population of western Indonesia obese who are obese.

Methods: In this study, we examined 178 subjects consisting of 89 who are obese with BMI> 25, and controls with BMI between 18.5 and 23. Fasting blood was taken from each subject for the examination of IL-6 and CRP levels by the ELISA method. Determination of genotype -174 G>C IL-6 gene was examined by Polymerase Chain reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) methods.

Results: The results of this study showed increased levels of IL-6 and CRP in the obese group compared to the controls. In the obese group, CC genotype had higher CRP and lower IL-6 levels than the GC and GG genotypes. The frequency of CC genotype in the obese group was 47.2% compared with 28.1% in controls and this genotype was considered a risk factor for obesity. Carriers of the C genotype as a dominant or a recessive model had greater risk of obesity.

Conclusion: It was concluded that the polymorphism -174G>C IL-6 gene is a risk factor for obesity and is associated with increased levels of IL-6 and CRP in an obese group of the Western Indonesian ethnic population.

KEY WORDS:
C-Reactive Protein, Interleukin-6, Inflammation, Obesity, Polymorphism, obesity

INTRODUCTION

Obesity is characterized by low-levels of inflammation or metabolic inflammation in immune cells, especially monocytes. White adipose tissue not only stores energy, but also is an active endocrine organ that secretes more than 50 cytokines/chemokines and bioactive mediators, predominantly interleukin-6 (IL-6) and C reactive protein in plasma.[1] Increased levels of IL-6 in obese patients not only occur during the acute-phase activation responses, but also modulate glucose metabolism, lipid metabolism and susceptibility to chronic disease.[2] C-reactive protein (CRP) is a reactant produced in the acute phase by the liver, as a marker of inflammation and is associated with body mass index (BMI), and obesity.[3] Polymorphism of interleukin-6 is associated with obesity, type 2 diabetes,[4] metabolic syndrome,[5] and ischemic stroke.[6]

Effects of polymorphism in the promoter region of IL-6 gene are known to differ among individuals in the amount of protein produced or systemic concentration in the response of inflammatory mediators. The polymorphism of G replaced by C in the promoter of the IL-6 gene (-174G>C) lies in the chromosome 7p21.[7] The polymorphism in the promoter of -174G>C IL-6 gene shows high transcriptional activity of the gene, while in other studies the result is still in conflict.[8,9]

Several studies have shown that G alleles are associated with comorbidities of obesity, but other studies show that C alleles are associated with obesity, and increase the risk of developing type 2 diabetes mellitus, hypertension, and cardiovascular diseases.[4,10] The variation of the IL-6 gene in the modulating of metabolic syndrome may be a consequence of a significant role in the aetiology of metabolic disease associated with obesity. Differences in some studies may be due to ethnic differences, as well as differences in lifestyle, food intake, and geographical location. Indonesia is a transcontinental country, where its territory consists of thousands of islands geologically considered as part of either Asia or Australia. There are two large ethnic groups in Indonesia: the western group of Indonesia is of Austronesian ethnicity and the eastern group

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of Indonesia is of Melanesian ethnicity, which are different in linguistics and biodiversity as well as genetic pool.[11]

This study aimed to determine the effects of -174 G>C IL-6 polymorphism as a risk factor of obesity and the levels of IL-6 and CRP in the Western Indonesian ethnic group. This research is expected to be the basis for improving the health of Indonesian people with obesity, both as a model of prevention and treatment.

MATERIALS AND METHODS

Subjects

This research used a case control study design consisting of 178 participants who were divided into two groups. The case group (obese) included 89 participants with a BMI of more than 25 kg / m^2 (female = 43; male = 46). Controls were 89 (female = 47; male = 42) people with normal BMI 18.5 - <25 kg/m^2 with the age of both ranging from 18 to 35 years. All participants signed informed consent forms, and the research was approved by the Medical and Health Research Ethics Committee Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada with the reference number: KE/FK/532/EC/2016. Subjects were excluded if they had infectious diseases, cancer, were lactating mothers, pregnant women, had liver or kidney disease, or subjects who take medications such as anti-hypertension, and hypolipidemic agents.

Anthropometric and Biochemical Measurements

Subjects had their weight and height measured to calculate their BMI. All measurements were measured by one person to avoid variations in the interpersonal measurements. Blood was taken after fasting for 8 hours. Blood samples (5mL) were centrifuged and separated into blood cells, buffy coat and plasma. Plasma was used to determine the C-reactive protein using ELISA DRG kits, and IL-6 concentrations were based on the ELISA KIT following the Human IL-6 Elabscience protocol.

Genotyping

DNA was extracted from the buffy coats of samples using the PROMEGA Kit, and then amplified using a primary design for the IL-6 gene promoter region. The primers were: 5'-TGACTTCAGCTTTACTCTTGT-3 '(sense) and 5'-CTGATTGGAAACCTTATTAAG-3' (antisense). The PCR cycle for amplification of the IL-6 gene promoter consisted of the following steps: denaturation, 1 minute at 95°C, 1 minute for primary annealing at 55°C, 1 minute for primer extension at 72°C, all in 30 cycles. The PCR product was digested by using the NlaIII restriction enzyme at 37°C for 4 hours, and then electrophoresis using 2% agarose gel. The C allele shown is denoted by 367 and 244 bp and G allele with 611bp.[12]

Statistical analysis

The Kolmogorov Smirnov test was used to determine the normality of data. The mean of BMI, CRP, and plasma IL-6 levels were compared between obese and control groups using unpaired T tests when the data were normally distributed. However, if the data were not normally distributed, then the data were transformed first. If still not normally distributed, the Mann-Whitney test was used. To compare the BMI, CRP and plasma IL-6 levels between the genotypes one-way ANOVA tests were used, followed by Post-Hoc tests. The genotype distribution in each group was tested by Chi-Square tests. Determination of Odds Ratio (OR) was done by using the Chi-Square test followed by the Yate's Correction test.

All statistical analyses were performed using SPSS 17 (Chicago, IBM).

RESULTS

Description the characteristics of participants are presented in Table I. There were significant differences in the body weight, BMI, waist and hip circumference, blood pressure, CRP and IL-6 level between obese participants compared to the controls.

The levels of plasma CRP and IL-6, among genotypes in obese and control subjects are presented in Tables II and III. Table II shows there were higher and significantly different CRP and IL-6 levels in all genotypes of the obese group compared to the controls. Table III shows the grouping of genotypes and comparison between obese and control groups. In the obese group, the highest CRP levels were found in the CC genotype and then the GC genotype with the lowest in the GG genotype. For the IL-6 levels in the obese group, the highest level was found in the GG genotype and then the GC and the lowest level was found in the CC genotype but in the control group, the levels of CRP and IL-6 were not significantly different in all genotypes.

Polymorphisms of -174G>C IL-6 gene as shown in Table IV found that there were higher frequency of CC genotype in the obese group than controls and lower GG genotype were found in the obese group than in control subjects. The CC genotype had a risk of obesity 7.39 times higher than the GG genotype and the CG genotype had a risk of obesity 4.4 times higher than the GG genotype. As a recessive model, the CC homozygote had a risk for obesity 2.29 times higher than other genotypes (GC+GG) and with the dominant model, CC + CG genotypes having a risk factor for obesity 5.19 times higher than the GG genotype. Additionally, subjects with C allele in -174G>C IL-6 gene had a risk for obesity 2.22 times higher than the G allele.

DISCUSSION

The main results of this study were: 1) obese subjects had higher blood pressure, CRP and IL-levels than controls; 2) in all genotypes, obesity contributed to increased CRP and IL-6 levels; 3) in the obese group, the CC genotype was the highest and had significantly different CRP levels and the lowest IL-6 level, but in the controls these levels were not significantly different in all genotypes; and 4) CC, and CG genotype and C allele were risk factors of obesity.

In this study, the higher plasma IL-6 levels in the obese subjects compared with controls are similar with previous research suggesting that IL-6 levels are positively correlated with BMI, as shown by the increased of CD163 marker macrophage in adipose tissue, as a marker for IL-6.[13] During obesity, adipocytes will increase in size of cells and adipose

Table I: Anthropometric and biochemical characteristics of obese and control subjects

Variable	Obese (n=89)	Control (n=89)	P
Men	46 (51.7%)	42 (47.2%)	-
Women	43 (48.3%)	47 (52.8%)	-
Age	22.1±4.1	21.3±4.0	0.217
Height (cm)	162.3±7.6	160.7 ±7.3	0.169
Body weight (kg)	81.9±14.6	53.37±8.11	<0.001
BMI (kg/m^2)	30.9±4.2	20.5±2.2	<0.001
Waist circumference (cm)	96.3±12.1	72.67±7.7	<0.001
Hip circumference (cm)	109.4±9.6	87.9±7.2	<0.001
Systole blood pressure (mmHg)	113.1±11.9	108.9±11.2	0.016
Diastole blood pressure (mmHg)	76.6±7.9	71.9±8.5	<0.001
CRP (mg/L)	2.26±2.13	0.49±0.52	<0.001
IL-6 (pg/mL)	5.51±2.68	3.05±2.03	<0.001

BMI = Body Mass Index; CRP= C-Reactive Protein; IL-6 = Interleukin-6

Table II: BMI ratio, CRP and IL-6 levels between obese and control subjects in -174 G>C IL-6 genotype

Variable	GG			GC			CC		
	Obese N=5	Control N=22	P	Obese N=42	Control N=42	P	Obese N=42	Control N= 25	P
BMI	27.8±0.8	20.7±2.0	<0.001	30.9±4.4	20.6±2.4	<0.001	31.5±4.1	20.3±1.9	<0.001
CRP	1.19±0.58	0.56± 0.61	<0.001	1.75±2.07	0.50±0.51	<0.001	2.90±2.15	0.42±0.47	<0.001
IL-6	8.49±0.55	3.11±1.41	<0.001	5.90±2.96	3.06±1.93	<0.001	4.76±2.20	3.00±265	0.005

BMI = Body Mass Index; CRP= C-Reactive Protein; IL-6 = Interleukin - 6

Table III: BMI ratio, CRP, IL-6 levels between -174 G>C IL-6 genotypes in obese and control subjects

Variable	Obese Genotype				Control Genotype			
	GG (n=5)	GC (n=42)	CC (n=42)	P	GG (n=22)	GC (n=42)	CC (n= 25)	P
BMI (kg/m^2)	27.8±0.8	30.9±4.4	31.4±4.1	0.18	20.7±2.0	20.6±2.4	20.3±1.9	0.70
CRP (mg/L)	1.19±0.58	1.75±2.07	2.90±2.15	0.023	0.56± 0.61	0.50±0.51	0.42±0.47	0.64
IL-6 ((pg/mL)	8.49±0.55	5.90±2.96	4.76±2.20	0.005	3.11±1.41	3.06±1.93	3.00±2.65	0.98

BMI = Body Mass Index; CRP= C-Reactive Protein; IL-6 = Interleukin - 6

Table IV: Frequency of -174G>C Interleukin-6 genotype in obese and control subjects

Variable	Obese (n=89)	Control (n=89)	OR (CI 95%)	P	H-W Equation	P
Genotype						
CC	42 (47.2)	25 (28.1)	7.39 (2.26-25.71)	0.0005	66	0.981
GC	42 (47.2)	42 (47.2)	4.40 (1.4-14.74)		85	
GG	5 (5.6)	22 (24.7)	1		27	
CC	42(23.6)	25 (14.0)	2.29 (1.17 – 4.48)	0.014		
GC+GG	47 (26.6)	64 (36.0)				
CC + GC	84 (94.4)	68 (38.2)	5.19 (1.73 – 16.65)	0.001		
GG	5 (2.8)	21 (11.8)				
Allele						
C	126 (35.3)	92 (25.8)	2.22(1.41-3.52)	<0.001		
G	53 (14.8)	86 (24.1)				

Frequency (%); OR = Odds Ratio; CI= Confidence Interval, H-W equation = Hardy-Weinberg equation

tissue will undergo changes in metabolism and immune response. Increase in the size of adipocyte contributes to the increase of IL-6 in circulation in obese individuals.[14] These results were also supported by research conducted by Braune et al.,[15] which found the expression of IL-6 gene and its receptor increased in the adipose tissue of obese mice. IL-6 has a role as a myokine, and in the skeletal muscle acts as an energy sensor by activating AMP-activated protein kinase (AMPK) and increasing glucose deposits, lipid oxidation, and lipolysis.[16]

This study showed obese subjects had higher levels of CRP than the control subjects. Research conducted by Boeta-Lopez et al.[17] also showed that CRP levels increased with increasing of BMI. The level of CRP in the blood is believed to be a lipid parameter, which can be identified as a risk factor of cardiovascular events. CRP expression is regulated at the level of transcription, and this process in the liver is induced by IL-6. Stimulation of IL-6 in the acute phase of inflammation, will increase plasma CRP levels.

The relationship of -174 G>C IL-6 gene polymorphism with IL-6 and CRP levels in this study showed that the obese group had higher CRP and IL-6 levels for all genotypes than controls; whereas in the obese group, GG genotypes had the lowest of IL-6 levels compared with GC and CC genotypes. In contrast to CRP levels, the highest level was found in CC genotypes compared to the GC and GG genotypes. Low levels of IL-6 occur because these polymorphisms occur in the promoter region and affect the transcriptional system. Polymorphism of SNP -174 G>C IL-6 gene is located near the C/EBP-binding site and GATA1 transcription factor1. This polymorphism produces a trans-activation reduction and decreases the ability of promoter to bind to the glucocorticoid receptors and promoters accessing GATA1 transcriptional repressors. IL-6 genes encode the sequence of 212 amino acids. The consequence of post-transcriptional modification in this gene is a truncated protein.[18] The effects of CC genotypes and C alleles in SNP -174 G>C IL-6 gene were significantly associated with lower plasma IL-6 expression or circulation compared with GG. The effects of -174G>C IL-6 gene polymorphism on CRP levels indicate that CC genotype in obese subjects had higher CRP levels compared with the GC and GG genotypes. This result is consistent with previous research in subjects of a family that were homozygous of CC genotype and had a significantly higher CRP levels compared to GG homozygous.[19] Carriers of C allele were found to have higher levels of CRP, which was a marker of an acute immune response compared with the G allele.[17]

In the obese group in this study, the C carriers had lower levels of IL-6, but higher levels of CRP than G carriers. These results were consistent with the role of IL-6 as an anti-inflammatory, anti-obesogenic agent, and its glucose homeostasis function. In the development of obesity, hepatic insulin resistance, hepatic inflammation, and mitochondrial dysfunction were observed in mice fed a high-fat diet with IL-6 deficiency.[20] IL-6 together with effector molecular pathways such as leptin control energy and glucose homeostasis through activation of STAT3 transcription factor. The activation of STAT 3 signalling by IL-6 in the hypothalamic neurons potentially suppresses appetite and increasing peripheral glucose homeostasis. Pharmacological and genetic approaches found IL-6 in the central nervous system works independently on the membranes of IL-6R.[21]

The polymorphism of -174G>C IL-6 gene in this study showed significant differences in the frequency of genotypes in obese subjects compared to controls. Frequency of CC genotype was higher and GG genotype lower in the obese group than in controls. The results of this study was similar to previous studies showing that genetic variation and the polymorphism of -174 G>C IL-6 gene play a role in the phenotype of obesity.[22] The role of IL-6 is involved in the homeostasis of energy through the regulation of central nervous system. Interleukin-6 mediates inflammation associated with cachexia via central mechanism and hypothalamic-pituitary-adrenal activation (HPA) axis in the hypothalamus level.[23] Contrary results found -174G>C IL-6 polymorphism did not have a significant effect on IL-6 levels, CRP levels, and BMI on non-obese subjects,[24] finding that -174 G>C IL-6 polymorphisms did not change the plasma IL-6 levels in the control subjects.

The frequency distribution of -174G>C IL-6 gene in this study showed CC genotype was more common in obese subjects than controls and this genotype had 7.39 times higher risk for obesity than the GG genotype while the GC genotype had 4.4 times higher risk for obesity than the GG genotype. The C allele has 2.22 times higher risk for obesity than the G allele. This result is in line with other research that found -174G>C polymorphism was a risk factor for obesity,[19,25-27] and cardiovascular disease.[28] The frequency measurement of the CC genotype in this research found 47.2% in obese and 28.1% in controls. This result was higher than other populations. Other studies on white American subjects found that 16% of CC genotype28, 15% in French Canadian[29], 6.2% in Iranian,[25] 25% and 11% in obese and controls of South African women30, with 7.3% and 2% in obese and controls of Romanian ethnicity.[23] The CC genotype was not found in African-American and black South African women.[30] This difference in the results indicates the differences in the gene pool for each ethnic group and populations and a different influence as a risk factor for the occurrence of obesity. This study needs further confirmation to determine the effects of -174G>C IL-6 polymorphism on certain nutritional factors that affect obesity and to examine the effect of the length of obesity on endothelial disorders that may cause chronic inflammation and contribute to the development of other diseases. Limitations of this study are the limitation in number of samples, and inability to control some confounding factors such as physical activity and diet.

CONCLUSION

The results support the conclusion that the polymorphism of -174 G>C IL-6 genotype in the ethnic people of Western Indonesia is associated with the increased risk of obesity, high plasma levels of IL-6 and C-Reactive Protein which are risk factors for other related diseases. Further, this research is expected to continue by examining the effect of gene variation on the giving of anti-inflammatory compounds which may have different effects on different genotypes, though the results can be used for specific genotypic purposes.

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