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The Association of Fat Mass and Obesity-Associated (FTO) rs9939609 Gene Polymorphisms with Leptin Levels in Obese Subjects

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ABSTRACT

Background: Obesity is a multifactorial disorder that involves intricate interactions between environmental and hereditary factors. Single nucleotide polymorphism (SNP) rs9939609 in the fat mass and obesity-associated (FTO) gene has been linked to an increased risk of obesity. The hormone leptin, an essential component of energy balance regulation, is highly expressed in obese people, which is indicative of increased fat mass; nevertheless, the physiological effects of leptin are frequently hindered by paradoxical leptin resistance. The purpose of this study is to investigate the relationship between FTO polymorphisms and leptin levels in obesity.
Methods: This cross-sectional study included 79 individuals aged 18-60 years with BMI ≥25 kg/m², recruited from Prof. dr. I.G.N.G. Ngoerah General Hospital. The enzyme-linked immunosorbent assay method was used to measure serum leptin levels. The FTO gene, containing the rs9939609 variant, was amplified using the polymerase chain reaction, and then the amplified DNA was sequenced to determine the genotype (AA, AT, or TT).
Results: A total of 53 females and 26 males were genotyped. Of the individuals, 32 (40.51%) were TT, 41 (51.90%) were AT, and six (7.59%) were AA. The one-way ANOVA test results showed that at least one genotype had significantly different leptin levels than the others (p=0.013). The post hoc Tukey HSD test revealed that obese people with the AA genotype had elevated levels of leptin (8.19±2.05 ng/ml) compared to the wild-type (p = 0.046). Obese people who carry at least one copy of A allele (AT) had lower levels of leptin (5.02 ± 2.08 ng/ml) compared to homozygous (AA) (p = 0.009).
Conclusions: Balinese obese patients with the AA genotype for the rs9939609 polymorphism had noticeably greater serum leptin levels than those of the TT or AT genotype which further contributes to dysregulated eating patterns leading to obesity.

Keywords: FTO, leptin, obesity, polymorphism, rs9939609.

INTRODUCTION

Obesity, a multifactorial condition linked to behavioral, environmental, and polygenic predispositions, demands more attention due to the burden it causes on rising rates of morbidity and mortality. The prevalence of these conditions has drastically climbed by more than 50% worldwide with an expected

2.6 billion overweight and obese people in 2020 and 4 billion in 2035 [1]. As many as 35.5% of Indonesians, or 64.4 million individuals, were overweight or obese in 2018, according to data from the Indonesian Central Bureau of Statistics. This number is still rising, especially among low-income households and those living in rural areas [2]. In addition to many other socioeconomic drawbacks, obesity dramatically raises the risk of cardiovascular and metabolic complications, as well as a decreased quality of life [3,4].

Genome-wide association studies (GWAS) have consistently reported that individuals with particular single nucleotide polymorphisms (SNPs) in the fat mass and obesity-related gene (FTO) are at a higher risk of gaining weight, developing obesity-associated traits and comorbidities [5,6]. Body mass index (BMI) as an indicator for diagnosing obesity is influenced by FTO rs9939609 gene polymorphism (T/A substitution) particularly in Asian populations [7,8]. The human FTO gene is 410,507 bases long and is found on the chromosome 16q12.2 area [9]. One region that encodes the FTO gene, which is regulated by the cycle of eating and fasting, is the hypothalamus. The obesity-risk A allele, situated in the FTO gene's first intron, was linked to changes in the hypothalamic expression of this gene and a predilection for high-fat, energy-dense diets [10]. Studies showed that carriers of the A allele report more frequent loss of control when eating and have a much higher BMI than those with the wild-type allele [11]. Compared to controls, individuals with the AA genotype had an odds ratio for obesity that was around six times greater [12].

FTO, in its protein form, is a member of the superfamily of nonheme iron oxygenases that are dependent on α-ketoglutarate and are crucial for maintaining energy equilibrium [13]. Adipokines, such as leptin, are also linked to the effects of the nuclear protein FTO on body weight, adipogenesis, and energy metabolism. The anorexigenic leptin hormone, which is released into the bloodstream by adipose cells, regulates food intake and energy balance through pathways in the central and peripheral nervous systems, hence affecting body composition and weight [14]. In the hypothalamus, FTO can colocalize with the long form of the leptin receptor (OBRb or LepRb), and FTO protein levels are known to be lowered by leptin [15].

The association between leptin and polymorphisms in the FTO gene remains inconsistent. According to a study conducted in Iran on an overweight population, those with the AA genotype had greater serum leptin levels than those with the TT genotype [16]. Higher leptin levels were also more significantly linked to the FTO gene's A allele in Dutch adolescents starting puberty [17]. A study conducted in Romania revealed contradictory findings. Children with obesity who carried the normal allele had higher leptin levels [18].

Population-specific variations in leptin levels can be caused by genetic architecture that differs among ethnic groups and populations. Research conducted across ethnic groups may increase knowledge of outcomes in diverse communities and provide new perspectives on the genetic variables influencing obesity propensity. Therefore, the objective of this study is to identify the connection between leptin as a modulator of body weight and the FTO gene polymorphisms due to the high obesity epidemic in Indonesia and the limited number of research on these matters.

MATERIALS AND METHODS

Study design and patients

This study involves 79 recruited subjects ranging in age from 20 to 60 with the BMI ≥ 25 kg/m^2. Prof. dr. I G. N. G. Ngoerah Hospital, Denpasar was a place for recruiting the subjects in this cross-sectional study. Consent was obtained from each patient before their involvement in the study. The research protocol was approved by the Medical Faculty's Ethics Committee at Udayana University (1460/UN14.2.2.VII.14/LT/2024).

Individuals with psychological disorders, major medical conditions, medications known to alter body weight, or impaired thyroid, liver, or kidney function were excluded.

Anthropometric and laboratory measurements

Anthropometric parameters were measured including body weight (kg), height (cm), BMI (kg/m2), waist circumference (WC) (cm), and hip circumference (HC) (cm). Blood samples from enrolled subjects were taken after a 12-hour fast. Levels of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured on Cobas C501 autoanalyzer (Roche Diagnostics, Germany). The levels of leptin in serum were determined using enzyme-linked immunosorbent assays (ELISA) kits (BT-LAB® E1559Hu, Shanghai, China) following the manufacturer's instructions and read in ELISA reader (Thermo Scientific MultiskanTM GO Microplate Spectrophotometer, USA).

DNA extraction, amplification, and FTO genotyping

Genomic DNA was isolated from two milliliters of EDTA tubes using the Jena Bioscience PP-237S (Thuringia, Germany) by following the manufacturer's protocols and concurrently kept at 20ºC. The experimental analysis for PCR was optimized for a 35 µl final volume containing GoTaq® Green Master Mix kit, forward primer, reverse primer, DNA templates, and nuclease-free water. The two primers designed for amplification of FTO (rs9939609) variants were: (forward (F): (5'-AACTGGCTCTTGAATGAAATAGGATTCAGA-3') and reverse (R): (5'-AGAGTAACAGAGACTATCCAAGT-3')). The amplification reaction was performed for 40 cycles in The Biometra® TProfessional Thermocycler (Analytik Jena, Germany). In order to visualize the amplified products under ultraviolet light, the DNA band of the FTO (rs9939609) gene was analyzed using the gel electrophoresis technique on a 1% agarose gel stained with ethidium bromide. All unpurified PCR products were submitted to PT Genetika Science for sequencing to facilitate genotyping.

STATISTICAL ANALYSIS

The research data were statistically analyzed utilizing the IBM Statistical Package for the Social Sciences (SPSS) version 25.0. The Kolmogorov-Smirnov test was used to confirm the normality of data distribution. The Independent T-test or the Mann-Whitney test were used to evaluate continuous data and then displayed as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were analyzed using the Chi-Square method (if the conditions are met) or the Fisher's Exact method and reported as counts (percentages). The results were presented as odds ratio. Hardy-Weinberg equilibrium (HWE) analysis was performed for rs9939609 SNP assay. Leptin levels among all genotypes of the FTO (rs9939609) gene were analyzed using the one-way ANOVA test with a post hoc Tukey HSD test. Body weight, BMI, waist and hip circumferences, and fasting blood glucose levels among all genotypes of the FTO (rs9939609) gene were analyzed using the Kruskal-Wallis test. All tests were performed in 2-tailed and $p < 0.05$ was confirmed to be statistically significant.

RESULT

Twenty-six males and fifty-three females were genotyped. Six people (7,59%) were homozygous for the obesity risk allele (AA) of the FTO rs9939609 polymorphism, 41 people (51.90%) were heterozygous (AT), and 32 subjects (40.51%) were wild type (TT). The overall frequency of the A allele was 0.335 and the T allele was 0.665. Genotype frequencies did not differ significantly ($\chi^2 = 2.125$; $p = 0.145$) from

Hardy-Weinberg equilibrium (HWE) expectations (AA = 11.2%, AT = 44.6%, and TT = 44.2%). The characteristics of study participants based on sex can be seen in Table 1.

Table 1 Demographic and Biochemical Characteristics of Subjects

Variable	Male n=26	Female n=53	p	95% CI
Age (years)	32.39 ± 9.20	49.86 ± 8.59	<0.001*	-14.304 – -4.829
Sex (n (%))				
Male	26 (32.9%)			
Female	53 (67.1%)			
Body weight (kg)	100.28 ± 22.16	78.59 ± 9.79	<0.001*	9.511 – 28.619
BMI (kg/m^2)	34.97 ± 6.44	32.98 ± 3.63	0.257	-1.223 – 4.416
Waist circumference (cm)	111.23 ± 11.66	100.91 ± 5.13	<0.001*	5.382 – 15.544
Hip circumference (cm)	112.86 ± 12.16	109.34 ± 6.83	0.674	-4.410 – 6.739
Fasting blood glucose (mg/dl)	89.28 ± 12.37	105.14 ± 43.36	0.338	-23.518 – 8.224
SGOT (mg/dl)	22.98 ± 12.48	17.96 ± 5.84	0.055	-0.074 – 7.288
SGPT (mg/dl)	30.87 ± 25.08	18.36 ± 7.60	0.027*	1.311 – 20.122
TC (mg/dl)	230.00 ± 36.01	193.00 ± 58.12	0.880	-38.838 – 9.878
TG (mg/dl)	162.53 ± 55.61	121.96 ± 49.64	0.244	-28.659 – 2.253
HDL-C (mg/dl)	41.67 ± 5.86	48.63 ± 13.42	0.530	-20.538 – 11.144
LDL-C (mg/dl)	175.33 ± 36.53	132.88 ± 54.72	0.208	-26.940 – 11.606
Leptin (ng/dl)	5.84 ± 3.03	5.16 ± 2.58	0.550	-0.838 – 1.561
FTO genotypes			0.217	0.249 – 0.460
TT	14 (53.8%)	18 (34.0%)		
AT	10 (38.5%)	31 (58.5%)		
AA	2 (7.7%)	4 (7.5%)		
* The significant p-values are <0.05.				

Female obese subjects had a higher body weight and waist circumference when compared to male participants (both $p < 0.001$). The distribution of FTO genotypes in both female and male obese subjects was not significantly different ($p = 0.217$). The most frequent genotype found in males was TT (53.8%) and in females was AT (7.5%). The rarest genotype found in both sexes was AA.

The association of FTO rs9939609 genotypes with leptin levels

According to the ANOVA test results, at least one genotype had significantly different leptin levels than the others ($p=0.013$). To ascertain which particular genotypes had substantially different means of leptin levels from one another, a post hoc Tukey HSD test was used. The association of FTO rs9939609 genotypes with leptin levels based on the Tukey HSD test is depicted in Figure 1. The obese subjects have been categorized into 3 groups based on their genotypes.

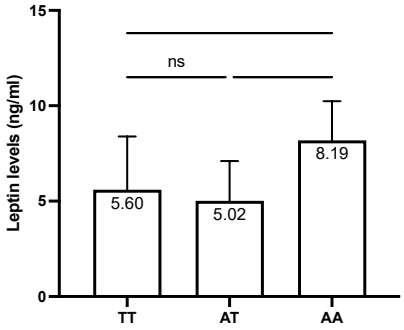

Figure 1. Leptin levels based on FTO rs9939609 genotypes

Obese people with the AA genotype showed elevated levels of leptin (8.19 ± 2.05 ng/ml) compared to the wild-type (5.60 ± 2.79 ng/ml) with p value = 0.046. Obese people who carry at least one copy of A allele (AT) had lower levels of leptin (5.02 ± 2.08 ng/ml) compared to homozygous (AA) (5.60 ± 2.79 ng/ml) with p value = 0.009. The mean leptin levels in all groups were

still classified as normal according to the International Diabetes Federation (IDF) [19].

The association of FTO rs9939609 genotypes with anthropometric measurements and fasting blood glucose levels

The Kruskal-Wallis test was used to detect the difference of means of body weight, BMI, waist circumference, hip circumference, and fasting blood glucose between each genotype group (Table 2). There was no discernible variation in the means of any of those parameters among all genotypes.

Table 2 The Kruskal-Wallis test results of body weight, BMI, waist circumference, hip circumference, and fasting blood glucose between each genotype group	
Parameter	p value
Body weight	0.365
BMI	0.935
Waist circumference	0.272
Hip circumference	0.613
Fasting blood glucose	0.892

The association of FTO rs9939609 genotypes with anthropometric measurements and fasting blood glucose levels is also shown in Figure 2.

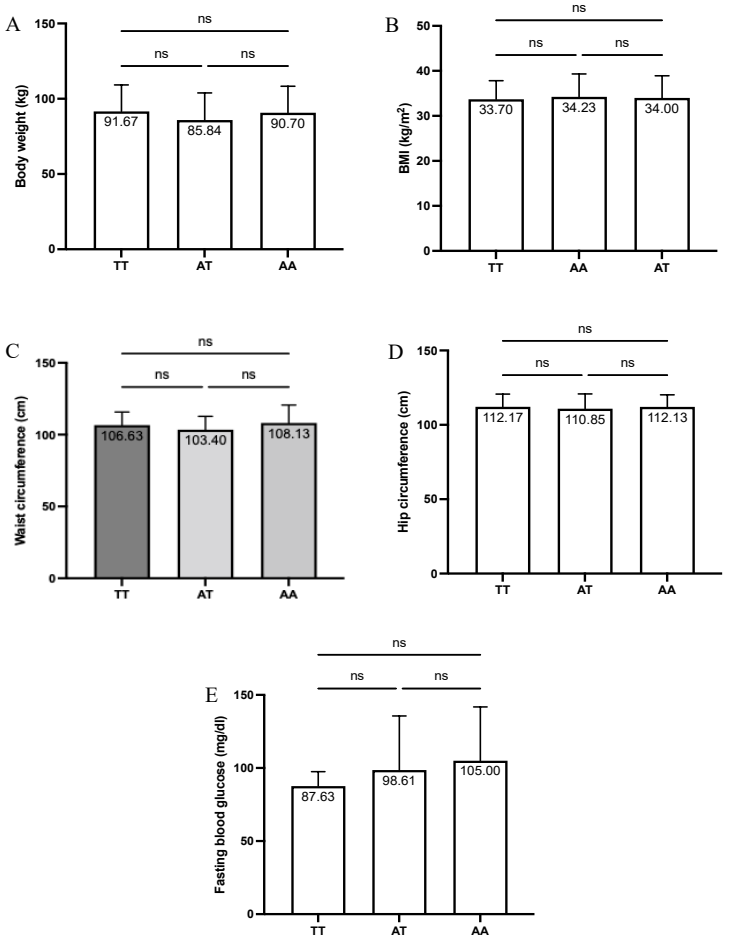

Figure 2. The association of FTO rs9939609 genotypes with body weight (A), BMI (B), waist circumference (C), hip circumference (D), and fasting blood glucose levels (E).

When we analyzed the anthropometrical (body weight, BMI, waist, and hip circumferences) and blood glucose parameters according to rs9939609 genotypes in the obese group, no significant associations were detected. A trend toward higher fasting glucose levels in the A allele carriers (AA and AT) as compared to TT genotypes was found, although it was not statistically significant ($p = 0.892$).

DISCUSSION

Obesity, characterized by the buildup of excess fat within the body, is known to develop as a result of physical inactivity and sedentary living patterns [20]. Several GWAS have identified over 750 loci that were linked to independent obesity genetic variants [21]. In this study, all of the obese participants had their predicted and observed genotype frequencies in equilibrium by the Hardy-Weinberg equation.

Leptin, a hormone that can successfully lower body weight and food consumption, is closely related to obesity. Leptin resistance is the inability of the hormone to exert its anorexigenic effects, despite the fact that obese people have higher blood levels of the hormone (hyperleptinemia) [22]. Research indicated a robust positive correlation between serum leptin levels in non-diabetic adults and obese individuals based on their weight, BMI, and body fat percentage [23,24]. In proportion to the number of fat cells, white adipose tissue (WAT) produces leptin, which binds to the brain's leptin receptors (LEP-R) to convey signals that boost energy expenditure and reduce nutritional intake. Consequently, the amount of circulating leptin falls during starvation, but it rises after being refed or overfed [25].

In this study, higher leptin levels were found in the risk allele (A-allele) of FTO rs9939609 polymorphism, particularly in the form of homozygous genotype. The AA genotype may have an impact on appetite control because A allele carriers may have a decreased sense of fullness and a greater desire to eat, which leads to increased energy intake and consequent weight gain [26,27]. Individuals with the AA genotype may have altered levels of appetite-regulating hormones like ghrelin (lower postprandial levels) and leptin (higher levels), further contributing to dysregulated eating behavior [28].

Contrary to expectations, the mean leptin levels in all genotypes in this study were classified as normal (between 4.1–11.0 ng/mL) based on the IDF. Leptin secretion is regulated by dietary consumption, body fat percentage, and a number of hormones [29]. The main modulator of leptin synthesis through the glucose metabolism pathway is insulin [30]. Long-term hyperinsulinemia is widely recognized to stimulate an increase in plasma levels of leptin [31]. Furthermore, insulin can suppress leptin release in adipocytes for a short time before having a secondary stimulatory impact due to metabolic alterations brought on by the insulin-induced rise in glucose uptake [32].

Although it is well known that obese subjects have elevated leptin levels, leptin levels can also be normal or lower than expected. A study indicated a relative leptin deficiency in obese people with severe metabolic syndrome, which means that their leptin production was less than anticipated given the amount of fat tissue present. Leptin levels are not always abnormally elevated in obese people (especially in those with BMI > 40 kg/m^2) [33]. Instead of leptin resistance, the excess body weight could be caused by a relatively low synthesis of leptin by the adipose tissue. Mice that are completely deficient in leptin (Ob/Ob mice) experience early-onset morbid obesity as a result of severe hyperphagia triggered by this satiety signal being absent [34]. The Ob/+ heterozygous mice exhibit higher fat mass and lower leptin levels [35]. Nonalcoholic steatohepatitis (NASH), glucose intolerance, hyperlipidemia, and obesity may also be favored by partial leptin insufficiency (Ob/+) in mice with excessive consumption [36]. People who are partially leptin-deficient and heterozygous for Ob gene mutations are more likely to be

overweight or obese [37]. Although there are instances of monogenic (single-gene) diseases that can result in severe obesity, mutations in the Ob (leptin-producing) gene are not the most prevalent cause of obesity [38]. Mutations in the leptin receptor gene (LEPR) or other genes also involved in the leptin signaling pathway can lead to polygenic obesity [39].

In this study, we discovered that leptin levels were considerably higher in obese subjects with the AA genotype than in those with the wild-type (TT) or AT genotype. Our findings are consistent with other studies showing a relationship between leptin levels and FTO rs9939609 polymorphism [40], but when adjusting for BMI this association vanished [17,41]. We also found no significant associations between FTO genotypes and BMI. It could suggest that this FTO rs9939609 polymorphism and leptin are more closely associated compared to BMI. The fact that FTO or its functional long-range targets [42] have a greater direct impact on fat mass and composition phenotypes—which leptin can more accurately reflect—than on total obesity may be one reason. Our modest sample size in comparison to big population-based GWAS may be another factor contributing to the lack of a relationship between FTO genotypes and BMI [43].

Moreover, we found that there were no significant associations between FTO genotypes and other anthropometric parameters (body weight, waist, and hip circumference). However, the study's male and female participants differed significantly in terms of body weight and waist circumference, with the females having a lower body weight. It is possible that body weight, BMI, and other anthropometric traits are regulated not only by a single FTO gene, but including a complex interplay of multiple genetic makeup, age, gender, level of physical activity, diet, and some environmental factors [44].

Additionally, no statistically significant associations were found between fasting blood glucose levels and FTO genotypes. However, there was a tendency toward higher levels of fasting blood glucose in AA and AT genotypes compared to the wild-type. Homozygous A of rs9939609 in a study involving subjects from the United Arab Emirates demonstrated statistically significant elevated fasting blood glucose along with a trend of elevated insulin and HOMA2IR, but not elevated BMI [45]. A study including young, healthy males from Denmark revealed similar results, showing that the FTO rs9939609 A-allele was linked to hepatic insulin resistance, increased fasting blood glucose, and plasma insulin [46]. This suggests that the genetic predisposition to obesity conferred by FTO can also influence glucose metabolism.

CONCLUSION

The homozygous genotype for the rs9939609 (AA) had significantly higher serum leptin levels than those with TT or AT genotype in Balinese obese subjects. The FTO gene's SNP rs9939609, specifically in the AA genotype, can alter appetite regulation and indirectly influence elevated leptin secretion, which further contributes to dysregulated eating patterns leading to obesity.

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflict of interest.

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