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Association between Adiponectin Gene rs2241766 Polymorphism and Dietary Patterns and Serum Adiponectin Levels among Javanese Adolescents with Obesity: A Cross-Sectional Study

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ABSTRACT

Objective: Adiponectin plays an essential role in the relationship between obesity and insulin resistance. This study aimed to analyze whether serum adiponectin levels are associated with adiponectin gene rs2241766 polymorphism and dietary patterns.

Methods: This cross-sectional study involved Javanese adolescents aged 13-18 years with obesity. Obesity was defined according to the centers for diseases control and prevention 2000 criteria. Blood samples were collected to determine serum adiponectin levels through enzyme-linked immunosorbent assay and adiponectin gene rs2241766 polymorphism through polymerase chain reaction restriction fragment length polymorphism. Dietary patterns were described using energy consumption percentages from carbohydrates and fat, calculated from a 24-hour dietary recall for 2 consecutive days.

Results: We included 240 adolescents with obesity. Genotype distributions of the adiponectin gene rs2241766 polymorphism were 61.3%, 34.6% and 4.2% for the TT homozygous, TG heterozygous and GG homozygous variants, respectively. The median serum adiponectin level was 13.9 (1.5-46.6) µg/mL.

Conclusion: Serum adiponectin levels were not significantly associated with higher fat or carbohydrate consumption and adiponectin gene rs2241766 polymorphism.

Keywords: Adolescents; Javanese; Adiponectin; ADIPOQ rs2241766; Polymorphism, Dietary pattern; Dietary recall; Carbohydrates; Fat; Obesity

INTRODUCTION

The prevalence rate of obesity among adolescents continues to increase annually. In 2013 in Indonesia, adolescents with obesity aged 13-15 and 16-18 years accounted for 2.5% and 1.6%, respectively, a figure that almost doubled by 2018. Given that adolescents with obesity are approximately five times more likely to become obese in adulthood, managing all factors that might cause obesity in adolescents is imperative to substantially reduce the overall burden of adult obesity.

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Presently, adolescents practice imbalanced nutritional habits (e.g., excessive consumption of sweetened beverages but less consumption of fruits and vegetables and insufficient physical activity), which are believed to be strongly associated with obesity. However, findings supporting such an association are still inconclusive. Genetic factors might play a role in body weight variations. Indeed, the Genome Wide Association Studies discovered over 40 genetic variations associated with obesity; one of them is adiponectin gene (*ADIPOQ*) polymorphism. Nonetheless, the *ADIPOQ* rs2241766 polymorphism could have heterogeneous impacts depending on ethnicity. In fact, one meta-analysis on adults showed that *ADIPOQ* rs2241766 polymorphism might be associated with obesity in Chinese individuals but not in non-Chinese. However, this research has never been conducted in the Javanese population [1-10].

ADIPOQ affects adiponectin production. Bahraini and Indian had attempted to prove that allele G of the *ADIPOQ* rs2241766 polymorphism is associated with lower serum adiponectin levels. However, studies from different populations have shown conflicting results adiponectin, a hormone produced by adipocytes, regulates blood glucose levels by increasing insulin sensitivity. Low serum adiponectin levels can promote insulin resistance, which can cause hyperglycemia. Moreover, insulin resistance may increase appetite, further aggravating the energy imbalance in adolescents with obesity [11-17].

Variance in *ADIPOQ*, dietary patterns and adiponectin levels has been related to each other. The variance in *ADIPOQ* accounts for differences in adiponectin production in response to a hypocaloric diet. To our knowledge, only few studies have investigated the influence of *ADIPOQ* Single-Nucleotide Polymorphisms (SNPs) (rs2241766) and dietary patterns on serum adiponectin levels in adolescents with obesity. Thus, this study aimed to analyze whether serum adiponectin levels are associated with *ADIPOQ* rs2241766 polymorphism and dietary patterns. The results of this study may help in obesity management by prescribing a specific diet based on genetic profiles [18,19].

MATERIALS AND METHODS

Research Participants

This cross-sectional study included adolescents with obesity enrolled in 12 junior and senior high schools in Surabaya and Sidoarjo city, East Java Province, Indonesia, from May to September of 2020. Participants were determined using a total population sampling method that satisfied the inclusion and exclusion criteria.

Minimum sample size was calculated using formula for estimating a population proportion with a specified absolute precision.

$$n = Z^2_{1-\frac{\alpha}{2}} P(1-P)/d^2$$

The minimal sample size is 97. The inclusion criteria were Javanese adolescents aged 13-18 years with obesity. Adolescents who had a history of corticosteroid consumption at least for 2 months or were sick or not fasting upon data aggregation were excluded from the study. This study conformed to the national and international ethics requirements in the conduct of research involving human beings, following the declaration of Helsinki. It was also approved by the ethics committee on research of Airlangga university (approval number: 115/EC/KEPK/FKUA/2020). Participants and parents/legal guardians provided written informed consent after being informed regarding the study. We also informed them that the results of this study will be published while keeping their information confidential during all sample processing and publication processes.

Anthropometric Measurements

Obesity was established according to the Centers for Diseases Control and Prevention (CDCP) 2000 criteria, which are based on BMI for age and sex above the 95th percentile. Body weight was measured using a digital weighing scale (Seca, Germany no ref. 224 1714009) with 0.1 kg precision. Subjects stood barefoot and wore thin clothing during bodyweight measurements. Height in meters was measured using a stadiometer (Seca, Germany no ref. 224 1714009), with 0.1 cm accuracy. During height measurements, the participants stood barefoot without using a hat. The stadiometer was used to measure the height from the heel to the vertex. Subsequently, the BMI was calculated using the following formula:

$$BMI = \frac{Body\ weight\ (kg)}{Body\ height\ (m)^2}$$

Genotyping of Adiponectin Gene Polymorphisms

ADIPOQ rs2241766 polymorphisms were genotyped using the Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) technique at the Institute of tropical diseases laboratory in Airlangga university. DNA was extracted from the peripheral leukocytes in ethylene Di Amine Tetra Acetic Acid (EDTA)-treated whole blood using a DNA extraction kit (QIAamp DNA Blood Mini Kit; Qiagen, Germany). The genotype of SNP+45T>G was amplified using PCR (Top Taq Master Mix Kit) to obtain 371 base pairs from exon 2 with forward primer 5'-GAAGTAGACTCTGCTGAGATGG-3' and reverse primer 5'-TATCAGTGTAGGAGGTCTGTGATG-3'.

PCR was conducted via initial denaturation at 94℃ for 5 minutes, followed by 32 PCR cycles of denaturation for 30 seconds and then annealing at 60℃ and extension at 72°C for 30 seconds. PCR results were presented as DNA fragments seen as a ribbon under ultraviolet light and documented using electrophoresis gel consisting of 2%-2.5% of agarose gel, 4 µL of ethidium bromide and 0.5 × Tris/Borate/EDTA buffer. The ribbons were then compared using a marker (3 µL of DNA (0.5 µg/µL), thermo scientific) and marker gen ruler 100 bp that had been added to the electrophoresis gel. Positive results were marked with a tape of appropriate size. RFLP was conducted by incubating the PCR product in a water bath containing the restriction endonuclease SmaI. After incubation, the electrophoresis process was performed again to identify *ADIPOQ* rs2241766 polymorphisms marked by excised PCR products at specific sites using the restriction endonuclease [20].

Dietary Pattern Evaluation

Dietary patterns were evaluated using a 24-hour dietary recall questionnaire for 2 consecutive days before data retrieval. In the interview for the dietary recall, we used a food model to help the participants estimate the portion of consumed food. All gathered data were then converted into total calories and amount of calories from carbohydrates, protein and fat according to the food exchange list. Next, we calculated the mean values of total calories and total macronutrient consumption from the 2 consecutive dietary recall days. The proportion of carbohydrates was calculated according to the amount of caloric intake in the diet process derived from carbohydrates divided by the total caloric intake multiplied by 100%. We used the same method to determine the proportion of proteins and fats in the diet [21,22]. Carbohydrate consumption was divided into the following three groups based on the percentage of the average energy intake:

- High-carbohydrate diet (>65%)
- Moderate carbohydrate diet (45%-65%)
- Low-carbohydrate diet (<45%)

Fat consumption was classified into two groups:

- High-fat diet
- Non-high-fat diet

High fat diet was defined as energy intake from dietary fat exceeding 30% of the total calories consumed [23].

Measurement of Serum Adiponectin Level

After an overnight fasting, 3 mL of blood samples were collected from each participant. Plasma adiponectin in µg/mL was measured using Enzyme-Linked Immunosorbent Assay (ELISA) kit (Diagnostics Biochem, Canada).

Statistical Analysis

All statistical data involving individual parameters were analyzed using the statistical software SPSS 21.0. Variables were described according to their type. Quantitative variables are presented as means and their Standard Deviation (SD), whereas nominal (categorical) variables are presented as absolute and relative (percentage) frequencies. The distribution of baseline characteristics (e.g., weight, height, BMI, fat proportion on diet and adiponectin) based on sex was analyzed using the Mann-Whitney U test. Other baseline characteristics with normal data distribution (e.g., total calorie consumption and dietary proportions of carbohydrate and protein) were analyzed using the t-test. We also used the Mann-Whitney U test to determine differences in serum adiponectin levels between genotype *ADIPOQ* rs2241766 polymorphisms. Moreover, mean differences in serum adiponectin levels according to carbohydrate and fat consumption were identified using the Kruskal-Wallis test (carbohydrate consumption) and Mann-Whitney U test (fat consumption). We used the same method for analyzing whether genotype *ADIPOQ* rs2241766 polymorphism and carbohydrate or fat consumption were associated with serum adiponectin levels.

RESULTS

A total of 424 adolescents with obesity were identified through screening. Among them, 178 were unwilling to participate in this study and 6 did not maintain the 12-hour fasting.

Ultimately, 240 adolescents with obesity (mean age, 181 ± 18 months; no significant difference in sex distribution, P=0.37) were included, among whom 54.2% were junior high school students and the rest were senior high school students. **Table 1** presents the characteristics of all eligible participants.

Table 1: Patient characteristics.

Variables	Boys	Girls	P
Weight (kg, mean ± SD)	87.4 ± 14.6	S	0.001
Height (cm, mean ± SD)	164.2 ± 7.9	156.9 ± 8.0	0.001
Body mass index (kg/m2, Mean ± SD)	32.4 ± 4.2	32.9 ± 4.7	0.541
Consumed calories			
Total (kilocalories)	2487 ± 418.9	2461 ± 414.1	0.642

Carbohydrates (%)	62.4 ± 10.9	61.0 ± 9.9	0.322
Fats (%)	21.4 ± 10.2	23.3 ± 9.3	0.071
Proteins (%)	15.4 ± 2.9	15.1 ± 3.1	0.392
Adiponectin (µg/mL)	14.8 ± 6.8	16.7 ± 8.4	0.091

Note: [1]Mann-Whitney U test; [2]t-test

Participants had a mean body weight of 84.5 kg ± 13.6 kg, height of 160.7 cm ± 8.8 cm and BMI of 32.6 kg/m^2 ± 4.4 kg/m^2. The mean of total calorie consumption per day was 2474.8 ± 415.9 kilocalories, of which 61.7% ± 10.5%, 15.3% ± 3.0% and 22.3% ± 9.8% were from carbohydrates, proteins and fats. Additionally, 15 (6.3%) and 97 (40.4%) participants had low and high carbohydrate consumption, respectively, whereas 42 (17.5%) had high-fat consumption (**Figures 1 and 2**).

The total mean serum adiponectin levels were 15.7 µg/mL ± 7.6 µg/mL. **Table 2** summarizes the serum adiponectin levels according to carbohydrate and fat consumption. Thus, the mean serum adiponectin levels showed no significant differences according to the dietary proportions of carbohydrates or fat.

Table 2: Serum adiponectin levels according to the dietary proportions of carbohydrates and fat.

	N (%)	Adiponectin (µg/mL) mean ± SD	P
Carbohydrate proportion on diet			
Low carbohydrate	15 (6.3)	17.8 ± 8.3	0.511
Moderate carbohydrate	128 (53.3)	15.5 ± 7.5	
High carbohydrate	97 (40.4)	15.7 ± 7.8	
Fat proportion on diet			
High fat	42 (17.5)	17.2 ± 8.3	0.142
Non-high fat	198 (82.5)	15.4 ± 7.5	

Note: [1]Mann-Whitney U test; [2]t-test

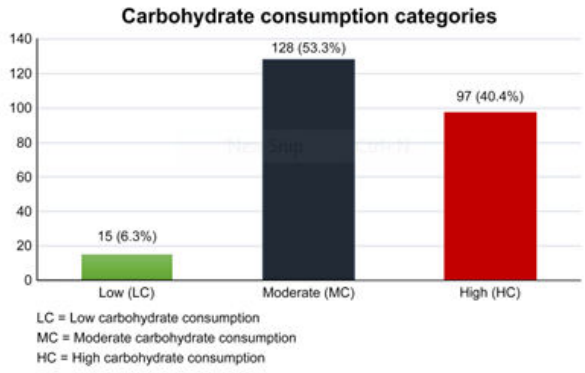

Figure 1: Results of the dietary recall on carbohydrate consumption.

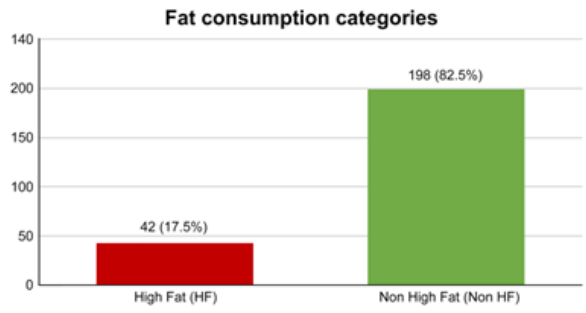

Figure 2: Results of the dietary recall on fat consumption.

The PCR-RFLP results for *ADIPOQ* rs2241766 polymorphism showed that among the participants, 147 (61.3%), 83 (34.6%) and 10 (4.2%) were TT homozygous, TG heterozygous and GG homozygous, respectively (**Figure 3**).

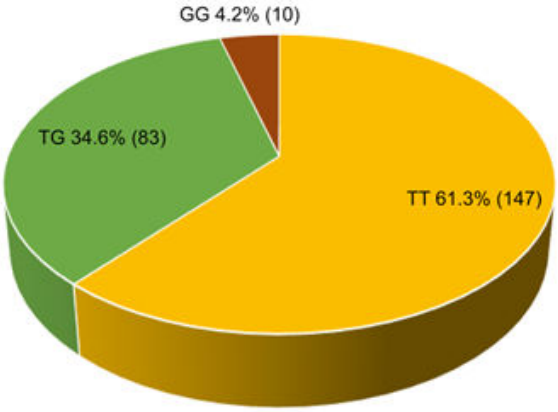

Figure 3: Genotype distribution of *ADIPOQ* rs2241766 among Javanese adolescents with obesity.

Therefore, 95.8% and 38.8% of our participants had the T and G alleles, respectively. Serum adiponectin levels based on the *ADIPOQ* rs2241766 polymorphism genotype revealed that those with the TT homozygous, TG heterozygous and GG homozygous genotypes had mean serum adiponectin levels of 15.5 ± 7.1, 15.7 ± 8.2 and 17.8 ± 10.1 µg/mL, respectively, with no significant difference (P=0.74). Furthermore, Table 3 describes the association of *ADIPOQ* rs2241766 polymorphism and dietary patterns (dietary proportions of carbohydrate or fat) with serum adiponectin levels. Accordingly, the mean serum adiponectin level revealed no significant differences according to *ADIPOQ* rs2241766 polymorphism and dietary proportions of fat or carbohydrate.

	Adiponectin µg/mL M ± SD	P
Carbohydrate proportion on diet		
TT homozygous		
Low carbohydrate	15.5 ± 6.0	0.441
Moderate carbohydrate	15.9 ± 7.1	
High carbohydrate	14.9 ± 7.4	
TG heterozygous		
Low carbohydrate	22.3 ± 11.0	0.081
Moderate carbohydrate	17.1 ± 14.9	
High carbohydrate	13.9 ± 11.8	
GG homozygous		
Low carbohydrate	-	0.521
Moderate carbohydrate	22.6 ± 15.6	
High carbohydrate	14.5 ± 5.5	
Fats proportion on diet		
TT homozygous		
High fat	17.1 ± 8.1	0.252
Non-high fat	15.1 ± 6.8	
TG heterozygous		
High fat	17.4 ± 8.6	0.232
Non-high fat	15.2 ± 8.0	
GG homozygous		
High fat	-	-
Non-high fat	17.8 ± 10.1	

Note: [1]Mann-Whitney U test; [2]t-test

DISCUSSION

Adiponectin is associated with specific triglyceride storage in the adipose tissue. The increase in adipose tissue depends on two processes, namely, adipogenesis (formation of mature adipocyte cell) and lipogenesis (adipocyte's ability to store triglycerides). One hypothesis stated that during positive energy imbalance, subcutaneous adipocyte tissues have a limited ability to increase their mass; therefore, excess fat will be accumulated as a visceral fat tissue. Several proinflammation cytokines excreted by visceral fat have been presumed to contribute to the decrease in adiponectin production. As such, triglycerides within adipocytes could originate from fats, carbohydrates or protein [24,25].

As shown in Table 2, adiponectin was not significantly associated with the dietary proportions of carbohydrates and fats, similar to the results of a previous study by Yannakoulia, et al. conducted among Greek adolescents without obesity. Likewise, Murakami et al. found no association between macronutrient consumption and serum adiponectin levels among Japanese women. However, Tayyem, et al., found that Jordanians with lower serum adiponectin levels had increased consumption of carbohydrate and water-insoluble fiber [26-28].

Adiponectin levels increase together with body weight. As suggested in the study by Song, et al., individuals consuming low fat and high-carbohydrate diet had decreased serum adiponectin levels. Similarly, our study found that the high-carbohydrate group had lower serum adiponectin levels than the low-carbohydrate group although the difference was not statistically significant. Summer, et al., suggested that a significant increase in adiponectin occurs with a low-carbohydrate diet but not with a low-fat diet [29,30].

In contrast to our findings, Kasim-Karakas, et al., showed that the high-carbohydrate low-fat diet group had significantly increased levels of serum adiponectin. This discrepancy might have been caused by the difference in participant population and types of carbohydrates and fats consumed by different races. Moreover, our study involved adolescents with obesity that was generally going through puberty, whereas the study by Kasim-Karakas involved post-menopausal women. Puberty hormones might have an impact on serum adiponectin levels [31].

Table 2 also shows that the high-fat diet group exhibited higher serum adiponectin levels than the non-high-fat diet group. This result was associated with not only the lower amount of carbohydrates consumed in the high-fat group but also the variety of consumed fats. High Monounsaturated Fatty Acid (MUFA) levels were previously reported to be more correlated with higher total adiponectin levels than with high-carbohydrate or high-protein consumption. In addition, Polyunsaturated Fatty Acid (PUFA) supplementation increased adiponectin levels while Saturated Fatty Acid (SFA) decreased serum adiponectin levels [32-35].

Obesity is characterized by increased BMI and disproportionate body composition resulting from increased fat mass. The irregular distribution of white adipose tissue is one of the pathologic processes in obesity. The accumulation of white adipose tissue depends on several risk factors, including environmental and genetic factors. Although the *ADIPOQ* rs2241766 polymorphism plays an important role in white adipose tissue distribution and regulation, the precise mechanism remains unknown [36].

The current study revealed that 61.3%, 34.6% and 4.2% of Javanese adolescents with obesity had TT homozygous, TG heterozygous and GG homozygous *ADIPOQ* rs2241766 polymorphisms, respectively. Interestingly, other ethnicities also provided similar results for *ADIPOQ* rs2241766 polymorphisms. A study of Mexican, Turkish, Roman, Chilean, French, Chinese and Thai populations showed TT homozygous to be the main genotype distribution. The composition of TG heterozygotes in these populations was approximately 19%-30%. Only 0%-5% of the populations had GG homozygous [37-40].

The adiponectin gene is located in chromosome 3q27. Meanwhile, the *ADIPOQ* rs2241766 polymorphism occurs on exon 2 from the locus and might affect adiponectin expression through mRNA instability [41]. In addition, we found no significant association between the genotype distribution of the *ADIPOQ* rs2241766 polymorphism and serum adiponectin levels, a finding similar to that presented in several previous Turkish, Greek and Malaysian studies. Nonetheless, other studies suggested opposite results.

In our study, the mean serum adiponectin levels were higher among those with the TG and GG genotypes, similar to the results of the studies conducted by Prakash, et al., Nascimento, et al., Lau and Muniandy and Guzman-Ornelas, et al. Conversely, Xita, et al. and Petrone, et al., showed that the mean serum adiponectin levels were higher among those with the TT genotype. These results were strengthened by evidence suggesting that the association between SNPs and the metabolic state is heterogeneous according to the population. The differing results between this study and others might have been caused by the diverse population.

Moreover, serum adiponectin levels were not associated with *ADIPOQ* rs2241766 polymorphism and the dietary proportion of fat and carbohydrates. Chung et al., was the first to suggest that *ADIPOQ* rs2241766 polymorphism and carbohydrate consumption influence serum adiponectin levels. They reported that the dietary intervention of replacing simple carbohydrates with complex carbohydrates and vegetables increased the serum adiponectin levels after 12 weeks in the TT and TG genotypes but not in the GG genotype. However, given that our study did not provide diet intervention, we could not describe the role of *ADIPOQ* rs2241766

polymorphism on serum adiponectin levels, which can be influenced by dietary patterns. Nonetheless, a high carbohydrate diet has been widely reported to reduce serum adiponectin levels in all genotype polymorphisms. In contrast, other studies found that serum adiponectin levels were not affected by food intake. However, people with high fat consumption had high serum adiponectin levels. This result might have been attributed to the lower-carbohydrate consumption in this group or the type of fat consumed. Moreover, SFA consumption would decrease serum adiponectin levels, whereas PUFA and MUFA consumption would increase gene expression associated with adiponectin production.

Excluding dietary patterns and *ADIPOQ* rs2241766 polymorphism, several factors can also influence adiponectin production. These factors include physical activity, pubertal state and *ADIPOQ* gene polymorphism in another locus. Unfortunately, given the limitations of our study, the aforementioned factors could not be determined. The 24-hour dietary recall carries a considerable risk of recall bias, possibly attributed to differences in the perception of food portions between researchers and respondents. To anticipate and decrease the risk of bias, we used a food model and 24-hour dietary recall for 2 consecutive days, which were effectively proven to reduce bias in previous studies. However, this method is fewer representatives of the daily calorie and macronutrient consumption over a long period of time [42-44].

This study determined whether *ADIPOQ* rs2241766 polymorphism and the dietary proportion of carbohydrates and fats are associated with serum adiponectin levels in Javanese adolescents with obesity. Our results confirmed that *ADIPOQ* rs2241766 polymorphism and dietary patterns were not associated with serum adiponectin levels in this population. Other factors that could influence serum adiponectin levels should be investigated. Further studies may also include participants without obesity and provide dietary interventions using the double blind method to observe the influence of gene polymorphisms and diet on serum adiponectin levels.

CONCLUSION

Javanese adolescents with obesity were found to have TT homozygous, TG heterozygous and GG homozygous *ADIPOQ* rs2241766 polymorphisms. In addition, the mean serum adiponectin levels showed no significant difference according to the dietary proportions of fat or carbohydrate and genotype variants of the *ADIPOQ* rs2241766 polymorphism.

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AUTHOR CONTRIBUTIONS

All authors conceptualized and designed the study. CF contributed to data acquisition, analysis and interpretation and initial manuscript construction. NAW and RI contributed to data collection and analysis, the review process and the final manuscript construction.

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CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

ETHICS APPROVAL AND INFORMED CONSENT

This study was performed in accordance with national and international requirements for the conduct of research involving human beings, following the declaration of Helsinki and was approved by the ethics committee on research of Universitas Airlangga with letter number no. 115/EC/KEPK/FKUA/2020. The participants and their parents were informed regarding the study and provided written informed consent.

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