International Journal of Technology

Volume 8 | Issue 2 | January 2017

www.ijtech.eng.ui.ac.id

Published by the Faculty of Engineering, University of Indonesia

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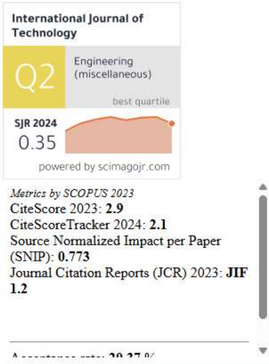
IJTech

p-ISSN : 2086-9614
e-ISSN : 2087-2100

Journal Metrics



Metrics by SCOPUS 2023
CiteScore 2023: **2.9**
CiteScoreTracker 2024: **2.1**
Source Normalized Impact per Paper (SNIP): **0.773**
Journal Citation Reports (JCR) 2023: **JIF 1.2**

IJTech is indexed in

JOURNAL ISSUE

07 Dec 2023
Volume 14, Number 7

International Journal of Technology 14(7) 1578-1585 (2023)
Received July 2023 / Revised September 2023 / Accepted November 2023

International Journal of Technology

http://ijtech.eng.ui.ac.id

Association between ADIPOQ (rs1501299) SNP with Insulin Resistance in Indonesian Type 2 Diabetes Mellitus Patients

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Abstract. Insulin resistance is an important aspect of metabolic endocrine disorder, and adiponectin functions as an insulin-sensitizer. Changes in adiponectin levels are associated with alterations in insulin sensitivity. Insulin resistance results from various variables that contributes to abnormalities in insulin signaling, including a decrease in adiponectin levels. Genetics is recognized as one of the key elements influencing adiponectin levels, with investigations showing that ADIPOQ SNP can impact insulin sensitivity and plasma adiponectin levels. Therefore, this study aimed to examine association between ADIPOQ gene polymorphism in patients with type 2 diabetes mellitus (DM) and insulin resistance level. A case-control study was conducted with 60 participants recruited from Sunyaragi Community Health Center in Cirebon, West Java. Data were collected using fasting blood glucose (mg/dl) and Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP). The results showed that the genotype frequency of SNP in the case group was GG = 12 (40%), GT = 16 (53.33%), TT = 2 (6.67%). Meanwhile, in the control group, it was observed to be GG = 18 (60%), GT = 11 (36.67%), and TT = 1 (3.33%). Statistically analysis showed a significant association between +276 G/T polymorphism and type 2 DM. This concluded that individuals with polymorphism are at higher risk of developing type 2 DM.

Keywords: Adiponectin; ADIPOQ; Insulin Resistance; SNP

1. Introduction

Insulin resistance is a pathological disorder affecting insulin-dependent cells such as skeletal cells and adipocytes, leading to a diminished response to normal levels of circulating insulin. This condition can give rise to various health complications, including hyperglycemia, hypertension, dyslipidemia, endothelial dysfunction, and metabolic disorders such as metabolic syndrome or type 2 diabetes mellitus (DM) (Yaribeygi *et al.*, 2019; Samuel and Shulman, 2016).

Obesity is a risk factor for insulin resistance, particularly in instances of excess fat accumulation. The metabolic effects associated with insulin resistance serve as valuable clinical indicators for identifying this condition (Sung *et al.*, 2018). Gold standard method for its detection include Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Homeostatic Model Assessment 2 (HOMA2), Quantitative Insulin Sensitivity Check Index

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doi: 10.14716/ijtech.v14i7.6691

(QUICKI), serum triglycerides, and the triglycerides to HDL ratio. Additionally, serum blood glucose levels are also used for the measurement.

The main effect of insulin resistance is development of type 2 DM. In this context, increased insulin production acts as a compensatory mechanism, leading to insulin resistance. However, pancreatic beta cells become damaged over time and are unable to meet insulin needs, resulting in hyperglycemia. Insulin resistance also contribute to other disorders such as metabolic syndrome, obesity, cardiovascular disease, nonalcoholic fatty liver disease, and polycystic ovarian syndrome (PCOS) (Condorelli *et al.*, 2017).

According to the International Diabetes Federation (IDF), an estimated 463 million individuals worldwide, aged 20 to 79, were diagnosed with DM in 2019. Southeast Asia ranks third with a prevalence of 11.3%, and Indonesia has approximately 1 million diabetics, as per the 2018 Basic Health Research conducted by (Ministry of Health Republic Indonesia, 2018).

The protein adiponectin, an insulin sensitizer encoded by ADIPOQ gene and released by adipose cells, plays a crucial role in reducing the rate of gluconeogenesis in the liver, enhancing the absorption of glucose, and maintaining insulin sensitivity. Single nucleotide polymorphisms, frequently called SNP, the most common type of genetic variation, can alter the transcription rate of mRNA, influencing protein production. SNP also has physiological impact on protein activity by changing the nucleic acid, thereby altering the type of amino acid produced. Insulin resistance can result from low plasma levels of the hormone adiponectin, influenced by various factors such as genetics, diet, exercise, and abdominal obesity (Moon *et al.*, 2014; Ziemke and Mantzoros, 2010).

Study in diverse population showed that SNP of ADIPOQ gene could influence the transcription rate or alter the amino acid sequence, consequently affecting plasma adiponectin levels and insulin sensitivity. However, this investigation have not been conducted in Indonesian. Despite that adiponectin operates as an insulin-sensitizer indirectly, when it experience a drop in the levels, there will also be a decrease in insulin sensitivity. This significantly plays a role in the formation of insulin resistance among type 2 DM patients. By investigating the alleles, genotype, and potential predisposition to type 2 DM in Indonesians, this study aims to contribute insights that could inform preventive strategies.

In accordance with the previous explanation, the focus is specifically on understanding how genetic factors, particularly ADIPOQ gene, affect insulin resistance. The purpose of this study is to examine association between ADIPOQ gene polymorphism in type 2 DM patients and insulin resistance levels in the Indonesian population.

2. Methods

2.1. Patient Selection

This study was an analytical observational case-control investigation comprising 30 case and 30 control subjects. Ethical approval was received from the Medical Faculty Research Ethics Committee at Swadaya Gunung Jati University (131/EC/FKUGJ/V/2022). The investigation was conducted at the Sunyaragi Community Health Center in Cirebon, West Java and the Faculty of Medicine's Laboratory of Genetics and Molecular Biology. The control group consisted of individuals without type 2 DM diagnosis, while the cases group met PERKENI criteria for type 2 DM within a 3-month period. Exclusion criteria included type 1 DM, cancer, autoimmune illnesses, and subjects on steroid anti-inflammatory medication. After patients have fasted for 8 hours, the fasting blood glucose levels was determined through proper examination.

2.2. Nucleic Acid Extraction

After initial screening of medical records and obtaining informed consent for sampling, 3 mL of peripheral blood was drawn in EDTA for genetic analysis. The TianGen TIANamp Hi-DNA/RNA Extraction Kit was used for blood extraction. The concentration and purity of DNA were assessed using the Maestrogen MaestroNano Pro Spectrophotometer. Finally, extracted DNA was stored at -20°C.

2.3. Genetic Analysis

DNA amplification was performed using BioRad T100 thermal cycler with forward primer: 5'-CCT GGT GAG AAG GGT GAG AA -3' and reverse primer: 5'-AGA TGC AGC AAA GCC AAA GT- 3'. The amplification protocol included denaturation at 95°C for 5 minutes, 35 cycles consisting of 95°C for 30 seconds, 65°C for 30 seconds, 72°C for 30 seconds, 72°C for 8 minutes, and ended with 25°C for infinity hold. A 2% electrophoretic gel confirmed the 241 bp PCR product using the BioRad GelDoc EZ Imager, to ensure that DNA has been amplified**.** After amplification, the product was cut with the BsmI restriction enzyme. Restriction results were analyzed by a 2% agarose gel to observe RFLP. The expected outcomes on the agarose gel were GG (Homozygous Wildtype) genotype cut to 95bp and 146bp, GT (Heterozygote) cut to 95bp, 146bp, and 241bp, and TT (Homozygous Mutant) cut to 241bp.

2.4. Data Analysis

The frequency of each genotype was calculated and presented as percentage. To determine association between the independent and the dependent variable, an unpaired t-test of >2 groups was used to compare the genotype at SNP +276 with the average GDP level. Polymorphism at +276 G/T with type 2 DM was evaluated using a contingency test with a 2x2 table to derive odds ratio and p-value.

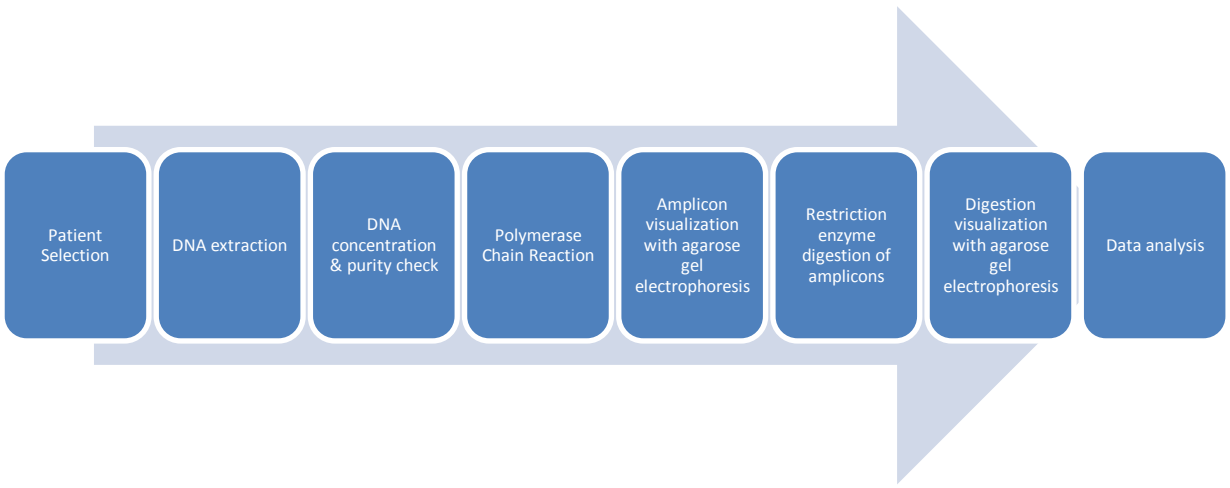


Figure 1 Schematic illustration of the workflow of the study

3. Results and Discussion

3.1. Patient Characteristics

This present study comprised 60 subjects, evenly divided into 30 cases and 30 controls, all meeting the predefined inclusion and exclusion criteria. Both body height and weight were measured with participants dressed in light clothing and without shoes. Obesity was assessed by body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters.

In the case group, 23 subjects fell under the normal body weight category, while 7 subjects were classified as overweight. Approximately 66% of the samples in this group showed increased fasting blood glucose levels. Meanwhile, the control had 10 overweights, and all subjects showed elevated fasting glucose levels (Table 1).

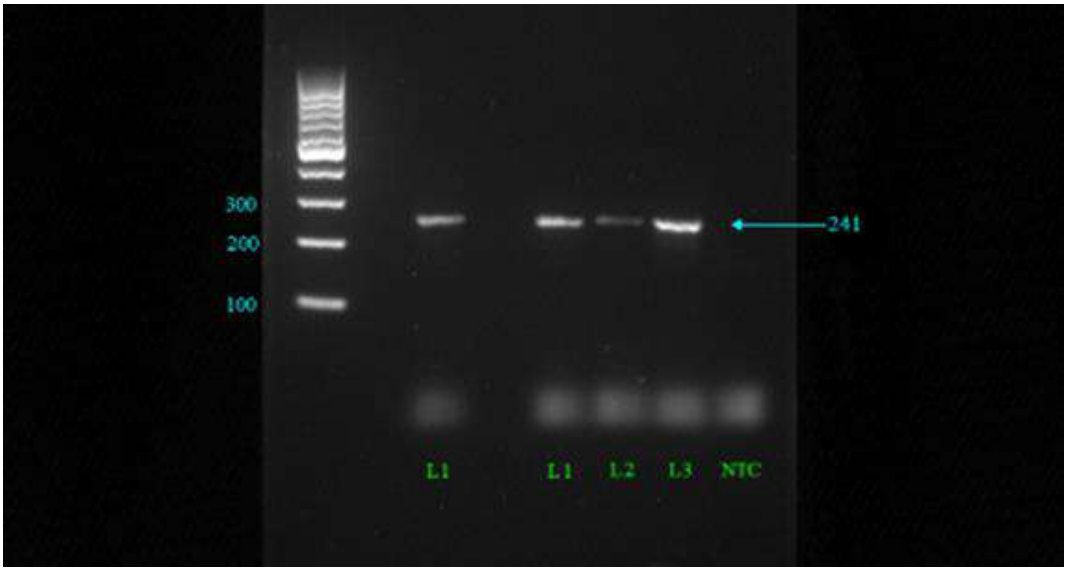
Table 1 Subject Characteristics based on age, sex, weight, height, BMI, and fasting glucose

	Case (n)	Control (n)	%
Age			
30-40	1	5	10%
41-50	5	10	25%
51-60	9	5	23.3%
61-70	10	5	25%
>71	5	5	16.7%
Sex			
Male	11	9	33.3%
Female	19	21	66.7%
Weight (kg)			
45-50	3	1	6.7%
51-60	8	8	26.7%
61-70	10	17	45%
71-80	8	4	20%
81-85	1	0	1.6%
Height (cm)			
150-160	6	4	16.7%
161-170	20	24	73.3%
171-175	4	2	10%
BMI			
Underweight	0	2	3.3%
Normal	23	18	68.4%
Overweight	7	10	28.3%
Fasting Glucose			
Normal	10	0	16.7%
Abnormal	20	30	83.3%

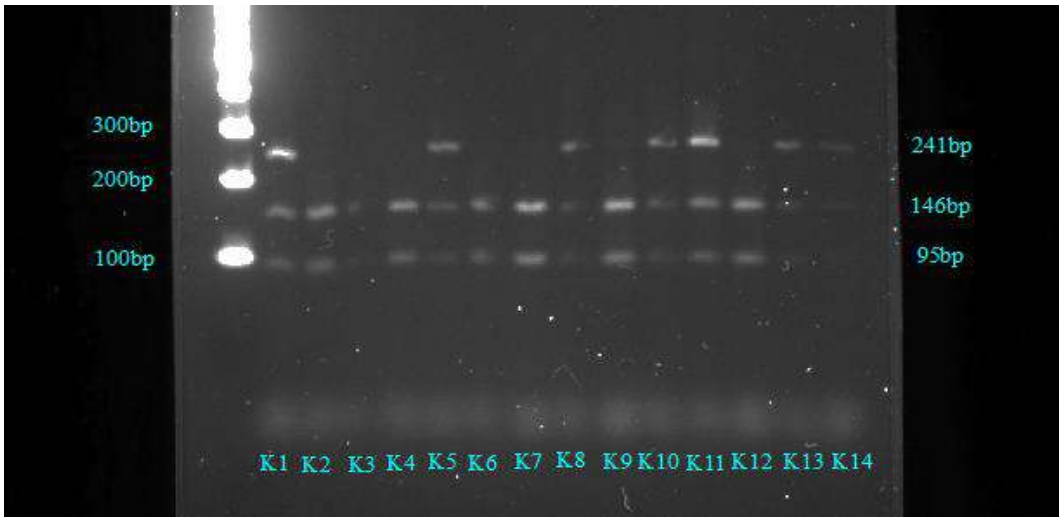
3.2. Genotypic Data

The results of PCR amplification are presented in Figure 2 (a), showing a band at 241bp from L1-L3, which corresponded to control sample 1-3 and non-template control (NTC) respectively. The results of the restriction enzymes were shown in Figure 1b. Furthermore, the uncut band at 241bp showed the presence of G allele, while cut bands at 146bp and 95bp showed the presence of T allele. In Figure 2 (b), subject K1 had bands at 241bp, 146bp, and 95bp, signifying the GT genotype.

Insulin resistance is an important aspect of metabolic endocrine disorder. Adiponectin functions as an insulin-sensitizer and changes in its level will also lead to alteration in insulin sensitivity. Insulin resistance occured as a result of various factors leading to abnormalities in insulin signaling, one of which is a decrease in adiponectin levels. Genetics is one of the elements influencing adiponectin levels. Several studies showed that ADIPOQ rs1501299 +276 G/T SNP increased the possibility of developing type 2 DM and insulin resistance (Yu *et al.*, 2018; Frankenberg, Reis, and Gerchman, 2017; Prakash *et al.*, 2015).



(a)



(b)

Figure 2 (a) PCR amplification results and (b) Restriction Enzyme digestion results. Figure 2(a) showed the PCR amplification result of 241bp prior to enzyme restriction (L1, L2, L3) and a non-template control (NTC) was added as a negative control. Figure 2(b) showed bands after restriction enzyme digestion where K1-K14 are control cases. K1 showed bands of 241bp, 146bp, and 95bp, which means one allele was cut by the restriction enzyme and the other was not, showing G and T allele and GT genotype

Despite +276 G/T SNP being a silent mutation, it converts G nucleotide base to T without altering the amino acid composition of the protein generated by ADIPOQ gene. Studies showed that ADIPOQ +276 G/T SNP affected adiponectin levels. Individuals with T allele have lower adiponectin levels and index of insulin resistance, despite lack of alteration in the protein (Yu *et al.*, 2018; Frankenberg, Reis, and Gerchman, 2017; De Luis *et al.*, 2017; Prakash *et al.*, 2015). This study aims to contribute to the existing body of knowledge by investigating association between the adiponectin gene, insulin resistance, and type 2 DM through fasting blood glucose levels.

The results of this study showed that the control had less polymorphism +276 G/T (21.7%), where the case group had more at 33.3%, as presented in Table 2. Examining the genotype frequencies of SNP +276 G/T in the case group indicated 12 (40%) GG, 16 (53.33%) GT, and 2 (6.67%) TT genotypes. Meanwhile, the control group had 18 (60%) GG,

11 (36.67%) GT, and 1 (3.33%) TT genotype, as presented in Table 3. It was also discovered that the case group had a lower frequency of GG genotype than the control, accompanied by a higher frequency of GT and TT genotypes.

Table 2 Allele frequency distribution

Allele	Cases		Control	
	n	%	n	%
G	40	66.7%	47	78.3%
T	20	33.3%	13	21.7%
Total	60	100%	60	100%

Table 3 Genotype frequency distribution

Genotype	Cases		Control	
	n	%	n	%
GG	12	40%	18	60%
GT	16	53.33%	11	36.67%
TT	2	6.67%	1	3.33%
Total	30	100%	30	100%

The results are similar with those of studies conducted in Chinese, Iranian, and Japanese population (Alimi, Goodarzi, and Nekoei, 2021). The analysis of SNP+276 G/T, with a p-value of 0.001, showed a significant association between SNP and the incidence of type 2 DM in Indonesian population. It was also shown that individuals with polymorphism had a 2.5 times higher risk of developing type 2 DM, as shown in Table 4.

3.3. Genotypic and Phenotypic Correlation

Table 4 Genotypic Association between ADIPOQ SNP and Type 2 DM.

Allele	Case (n)	Control (n)	OR	p-value
GT/TT	18	12	2.5	0.001
GG	12	18		

Table 5 Association between ADIPOQ SNP and mean Fasting Blood Glucose Levels

Genotype	Case (n)	FBG ± SD (range) (mg/dl)	p-value
GG	12	124 ± 112 (110-342)	
GT	16	230 ± 108 (116-460)	0.054
TT	2	127 ± 26 (110-144)	

The results were not in line with studies in the Arab and Korean population, where no association between SNP was identified, with a p-value of 0.69 (Nam *et al.*, 2018). However, they were in line with the Japanese and Chinese population with a p-value of 0.002 (Zhao *et al.*, 2016). Due to various demographics and the limited number of samples, variations from earlier investigations may occur. Previous genetics studies in Indonesia underscored differences in genetic makeup compared to more established populations (Nauphar, Wahidiyat, and Ariani, 2022; Pratamawati, Alwi, and Asmarinah, 2022). Therefore, it is advised that future investigations should be conducted using a wide number of samples. In addition to showing a 2.5 times higher risk in individuals with T allele, allele analysis at SNP+276 G/T showed a significant connection between the gene variant and the incidence of type 2 DM, as shown in Table 4.

No significant differences were observed between the genotypes of +276 G/T polymorphism in ADIPOQ gene in the case group with fasting blood glucose levels. A p-value of 0.054 was discovered in the statistical analysis, showing that there was no statistically significant difference between the 3 types of genotypes examined (Table 5). In the study by

(Al-Daghri *et al.*, 2012), similar results regarding association between GDP levels and genotype were obtained, with a p-value of 0.59.

This study has a primary limitation, stemming from the absence of plasma adiponectin level data, which could influence insulin resistance levels. Furthermore, the HOMA-IR examination, typically used for assessing type 2 DM levels, was not applied in this investigation. Consequently, a direct link between SNP +276 G/T and insulin resistance cannot be established. It is important to note that other genes, such as GLUT4 and IRS, had stronger connections to insulin resistance and type 2 DM.

4. Conclusions

In conclusion, approximately 60% of participants in this study who had type 2 DM experienced a polymorphism of +276 G/T. In the case group, the distribution of SNP +276 G/T genotype was 12 (40%), 16 (53.33%), and 2 (6.67%) with GG, GT, and TT genotype, respectively. In the control group, the breakdown was 18 (60%), 11 (36.67%), and 1 (3.33%) for GG, GT, and TT genotype concerning SNP +276 G/T genotype. Statistical analyses showed a significant association between the +276 G/T polymorphism and type 2 DM. However, the odds ratio value suggested that individuals with +276 G/T polymorphism were 2.5 times more easy to have developed type 2 DM. To present a more comprehensive understanding of the predisposed risk in the Indonesian population, future studies should include a larger number of subjects in this demographic to determine allele frequencies accurately.

Acknowledgments

The authors are grateful to the Universitas Swadaya Gunung Jati 2022 Internal Research Fund for funding this study.

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