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by Jems K. R. Maay

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Original Research Article

Correlation of E23K gene KCNJ11 polymorphism as a risk factor for obesity with type 2 diabetes mellitus in Jayapura, Papua

Jems K. R. Maay^{1*}, Pramudji Hastuti², Ahmad H. Sadewa²

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¹Doctoral Program of Medicine, ²Department of Biochemistry, Faculty of Medicine Public Health and Nursing, University of Gadjah Mada, Yogyakarta, Indonesia

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***Correspondence:**

Dr. Jems K. R. Maay,

E-mail: jemskrmaay@yahoo.co.id

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ABSTRACT

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Background: Pathophysiology of type 2 diabetes mellitus (T2DM) is influenced by the complex interaction of several genes that regulate energy metabolism in the body. Several polymorphisms that occur in many gene encode components of glucose metabolism regulation are significantly implicated in the onset of T2DM.

Methods: This case-control study. Case group with 58 subjects of T2DM patients with obesity and a control group with 58 subjects of non-DM obese patients from ethnic Papuans in Jayapura city, Indonesia.

Results: The results of the genotype frequency distribution (AA, GA, GG) and allele (A and G) showed statistically no significant differences. The relationship of anthropometry and blood chemical parameters with genotype (AA-GA-GG) gene potassium inwardly rectifying channel sub family J member 11 (KCNJ11) showed no statistically significant difference ($p > 0.05$). The relationship of anthropometry and blood chemical parameters of genotype (AA-GA) gene KCNJ11 indicated that diastolic blood pressure variables, glucose, triglyceride, high density lipoprotein (HDL), insulin levels, homeostatic model assessment (HOMA) β , and insulin resistance (IR) had statistically significant differences.

Conclusions: There is no difference in frequency between genotypes and alleles of the gene KCNJ11 in the T2DM and non-DM group with obesity. There is a link between genotypes of the gene KCNJ11 and T2DM occurrence. As for the combined analysis between blood chemical parameters and genotypes of gene KCNJ11, there is a relationship between genotypes of the gene KCNJ11 and the incidence of T2DM in LDL variables, where the coefficient interval value increases in patients with T2DM.

Keywords: Obesity, Type 2 diabetes mellitus, Gene KCNJ11, Polymorphism

INTRODUCTION

Papua Province is one of the provinces in Indonesia that has experienced a very rapid increase in population density. Along with this growth, the economy has also increased rapidly, affecting the level of prosperity and causing changes in people's lifestyles.¹ Papua Province, with an area of 319,036 km², consists of one (1) city and twenty-eight (28) districts with a population of 4,224,232 people. Since the enactment of the Papua Special Autonomy Law in 2001, the central government has provided governance and development policies to enable the achievement of people's welfare, especially for

indigenous Papuans (OAP). Changes in the lifestyle and activities of the Papuan people during the special autonomy era drastically altered the past lifestyle and diet, where previously the Papuan people consumed a lot of sago and tubers and were diligent in gardening and fishing.²

According to the regional health research (Riskesdas) in Papua Province, the prevalence of obesity in adolescents aged 16-18 years is in the very obese category, namely 2% very obese and 14.0% obesity above the national prevalence.³ The national prevalence is 7.3% consisting of 5.7% obesity and 1.6% very obese. In Papua Province, the

prevalence of obesity is 10.0%, and in 2018 it increased to 20.1%.⁴

According to a World Health Organization survey, Indonesia ranks fourth with the largest number of people with diabetes mellitus in the world after India (19.5%), China (16%), and the United States (13.9%). The prevalence of diabetes mellitus in Indonesia is estimated to reach 12.4 million people in 2025, almost a three-fold increase compared to 1995, 4.5 million people.⁵ According to Suyono the increase in the number of people with type 2 diabetes mellitus (T2DM) globally is due to an increase in prosperity and changes in lifestyle.¹ In Papua Province the prevalence of diabetes T2DM was 0.8% in 2013 and in 2018 it increased to 1.20%.^{3,4}

T2DM genetics is influenced by the complex interaction of several genes that regulate energy metabolism in the body. Polymorphisms that occur in many genes encoding proteins that regulate glucose metabolism have significant implications for the onset of T2DM.⁶ The genome-wide association study (GWAS) reports that potassium inwardly rectifying channel sub family J member 11 (KCNJ11) risk factors for T2DM disease.⁷ One of the important cell components in glucose metabolism is the potassium-adenosine triphosphate (K-ATP) channel in pancreatic β cells. This integral protein functions to regulate insulin secretion. Damage to these proteins can result in hyperinsulinemia and hyperglycemia. The K-ATP channel integral protein is encoded by two genes, namely KCNJ11 which encodes the subdomain Kir6.2.^{8,9} The KCNJ11 gene encodes a protein with 390 amino acids. In the substitution, the amino acid glutamate (E) is replaced with the amino acid lysine (K) at codon 23. The KCNJ11 gene is said to be responsible for reducing KATP sensitivity so that calcium channels open for a longer time, so that calcium enters the cell membrane and inhibits insulin secretion. Additionally, several studies have shown a correlation between the E23K gene and T2DM. Research showed the KK homozygous genotype has a significant relationship with T2DM in the Caucasian population and the EK heterozygous genotypes have a significant relationship in patients with T2DM and healthy populations.¹⁰ This research was conducted to analyze whether there are polymorphisms of (glu) E23K (lys) gene KCNJ11 as risk factors for T2DM in ethnic Papuans in Jayapura.

METHODS

This research was conducted in 7 (seven) public health centers in Jayapura city area (Eli Uyo public health centers, Waena public health centers, Raja kota public health centers, Tanjung Ria public health centers, Hamadi public health centers, Abepantai public health centers, Skouw public health centers) Papua province. The research will be conducted from March 2020 to June 2020. The research design was a case-control study. The case group was obese patients with T2DM and the control group was obese non-diabetic patients of ethnic Papuans in the city of Jayapura. Total samples were 116 (58 samples of obese T2DM

patients) and (58 samples of obese non-DM controls). This research was conducted in seven health centers in the Jayapura city area. Anthropometric measurements and body fat were measured using bioelectrical impedance analysis (BIA).⁵

The diagnosis of T2DM is confirmed by fasting plasma glucose levels ≥ 126 mg/dl (7.0 mmol/l) or plasma glucose levels ≥ 200 mg/dl (11.1 mmol/l) and blood glucose levels after 2 hours of glucose release 75 grams ≥ 200 mg/dl (11.1 mmol/l).¹¹ Measurement of GDP and G2PP levels used the glucose oxidase-p-aminophenazone (GOD-PAP) method, measuring triglyceride levels used the glycerol phosphate dehydrogenase-aminophenazone (GPO-PAP) method, and measuring total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) cholesterol used the cholesterol oxidase method with para-aminophenazone (CHOD-PAP).

Polymorphism E23K gene KCNJ11 was determined by the polymerase chain reaction (PCR) method, on deoxyribonucleic acid (DNA) samples obtained from the isolation of the blood buffy coat section. PCR cycle conditions were as follows: initial denaturation at 94 °C (7 minutes), 35 cycles of denaturation at 94 °C (1 minute), annealing at 60 °C (1 minute), extension at 72 °C (1 minute), and final extension at 72 °C (7 minutes). Initial denaturation at 95 °C (6 minutes), denaturation of 35 cycles at 94 °C (1 minute), annealing at 60 °C (1.5 minutes), extension at 72 °C (2 minutes), and final extension at 72 °C (10 minutes). The primers used were: forward primer 5'-CCACCGAGAGGACTCTGCA-3' and reverse primer 5'-CTG GCGGGCACGGTACCT-3'.

The results of DNA digestion by the restriction enzyme BanII were electrophoresed on 2% agarose gel visualized with fluorosafe. Electrophoresis lasted for 30 minutes, at 100 volts, and the results of the cutting was seen under UV light. The GG (wild type) genotype was not cut off so that there was 1 band of 179 bp. The GA genotype typically will have 3 bands, namely 179 bp, 160 bp, and 19 bp (invisible), while the AA genotype has 2 bands, namely 160 bp and 19 bp (not visible).

Statistical analysis of data collected was performed using Analyse-it v3.0 statistical software for Microsoft excel. Data collected was analysed by frequency, mean, standard deviation and chi-square test. For all statistical tests, the threshold of significance is fixed at 5%.

Statistical analysis of the collected data is performed using statistical package for the social sciences (SPSS) statistics version 22 for Microsoft excel.

The collected data was analyzed based on frequency, average, Independent t-test test, Mann-Whitney test, Chi-square test, analysis of variance (ANOVA) and Kruskal Wallis test. For all statistical tests, the significance threshold is set at 5%.

RESULTS

This study involved individuals with a history of T2DM with obesity (cases) and individuals with non-DM obesity (controls) with demographic data obtained from medical records (public health center records) and the results of blood glucose tests conducted at Prodia Laboratory, Jayapura city. The results of the independent t-test for the distribution of the characteristics of the anthropometric parameters showed that there was no significant difference between sex, age, bodyweight (wt), height (TB), systolic blood pressure, body fat (FAT), subcutaneous (SC), trunk, arms, legs, whole body, visceral fat (visceral fat), resting metabolism (RM), and body mass index (BMI). Diastolic blood pressure variables showed significant differences in cases and controls. The characteristics of anthropometric parameters can be seen in (Table 1).

Independent t-test results for variables of glucose, triglycerides, HDL, insulin levels, HOMA β , and HOMA IR indicating that there were significant differences in cases and controls. The results of the independent t-test for variable cholesterol, LDL, showed no significant difference (Table 2).

Results of the chi-square test for cholesterol, HDL, LDL, and HOMA β variables were not statistically different between the case and control groups. The variables of insulin, glucose, triglycerides, and HOMA IR >2.7 were significantly different between the case and control groups. Bivariate analysis showed that subjects who had abnormal/high insulin were 2.55 times more likely to develop DM compared with subjects with normal insulin with p value <0.001 . Bivariate analysis showed that subjects who had abnormal/high glucose were 236.0 times more likely to develop DM compared to subjects with normal glucose with p value <0.001 (very significant statistically).

Bivariate analysis showed that subjects who had abnormal/high triglyceride values were 3.608 times more likely to develop DM compared with subjects who had normal triglycerides with $p>0.002$. Bivariate analysis showed that subjects who had HOMA IR >2.7 normal 12.278 times more likely to develop DM compared with subjects who had HOMA IR 2.7 low with $p>0.001$ (Table 3).

Frequency distribution of genotypes (AA, GA, GG) and alleles (A and G) of KCNJ11 genes DMT2 obese and non-obese DM patients in ethnic Papuans in Jayapura city (Table 4 and 5).

Genotype frequency distribution (AA, GA, GG) of KCNJ11 gene in obese DMT2 patients (cases) and non-DM patients with obesity (control) there was no significant difference ($p=1$). Between the allele frequency distribution (A and G) of the KCNJ11 gene in obese and non-T2DM patients with obesity there was no significant difference ($p=0.881$). Odds ratio (OR) results to determine the risk

factors for T2DM with obesity were 1.00 (IC=0.061-16.379). The OR results to determine the risk factors for T2DM with obesity in the A allele were 0.914 (IC=0.508-1.645) (Table 4).

The results of the Chi-square test showed that there was no statistically significant difference in the frequency distribution of the KCNJ11 genotypes between the observed value and the expected value ($p=1$) in the study subjects based on the chi-square equilibrium equation. Table 5 shows the results of the chi-square analysis of the KCNJ11 genotype between the observed value and the expected value in the research subjects (Table 5).

The relationship between KCNJ11 genotypes and the incidence of T2DM and non-DM with obesity in ethnic Papuans in Jayapura city (Table 6 and 7).

The genotyping results of the KCNJ11 gene E23K polymorphism can be seen in (Figure 1).

Table 6, a sample screening of the research data for home value measurement β obtained several samples whose value >600 and <7 . So these values are categorized as outlier values (values that must be issued). Other variables do not output outlier values so DM obese $n=57$ and non-DM obese $n=57$. The results of blood chemical parameters with genotype (AA-GA and AA-GA) gene KCNJ11 with T2DM with obesity and non-DM with obesity in ethnic Papua in Jayapura city for variable LDL genotype AA-GA statistically showed a meaningful difference in T2DM patients with obesity, a p value of 0.023. While the HOMA variable β the AA-GA genotype showed there was a significant difference in T2DM patients with obesity, the value $p=0.013$.

In Table 7, the results of the relationship between blood chemistry parameters and genotype (AA-GA) gene KCNJ11 with the occurrence of DMT2 with obesity and non DM with obesity in Papua ethnic in Jayapura city showed that there was no meaningful difference between cholesterol and HDL. Independent t-test results for glucose variables between AA-GA genotypes showed significant differences between type 2 DM patients with obesity and non DM type 2 patients with obesity, $p=0.001$. The variable triglyceride genotype AA indicates there is a meaningful difference, the value $p=0.008$, while the variable triglyceride genotype GA shows there is a meaningful difference, the value $p=0.035$. The HDL variable genotype AA indicates there is a meaningful difference, the value $p=0.002$. Variable insulin levels of genotype AA indicate there is a meaningful difference, the value $p=0.001$. HOMA variables β genotype AA showed no meaningful difference, the value $p=0.001$, while the variable HOMA β genotype GA showed no meaningful difference, the value $p=0.003$. Statistically for the variable HOMA IR genotype AA-GA shows there is a significant difference in type 2 DM patients with obesity and non DM type 2 with obesity, the value $p=0.001$.

Table 1: Characteristics of anthropometric parameters in T2DM patients with obesity and non-DM patients with obesity.

Variable	DM type 2 obesity (n=58)	Non-DM obesity (n=58)	P value
	Median (95% CI)	Median (95% CI)	
Gender			0.843
Male (%)	20 (34.5)	18 (31.0)	
Female (%)	38 (65.5)	40 (69.0)	
Age (year) mean±SD	55.04±10.5	51.26±10.33	0.049
Body weight (BB) (kg)#	69.2 (66.0-72.7)	68.25 (65.0-72.5)	0.533
height (TB) (cm)#	155.0 (154.0-156.0)	157.0 (154.0-157.0)	0.498
Systolic blood pressure (mmHg #)	120.0 (115.0-128.0)	113.0 (110.0-120.0)	0.060
Diastolic blood pressure (mmHg)#	85.0 (80.01-90.0)	80.0 (78.0-81.0)	0.005*
FAT mean±SD	34.41±5.76	34.97±6.00	0.609
Sub cutaneous (SC)#	31.0 (29.3-32.4)	32.1 (30.1-33.5)	0.520
Trunk#	26.9 (25.6-28.7)	28.0 (26.3-29.35)	0.365
Arm#	45.5 (43.8-47.6)	47.5 (44.65-48.7)	0.190
Leg#	40.0 (37.9-41.95)	42.9 (38.6-43.6)	0.315
Whole body (WB)#	23.7 (23.1-24.3)	23.1 (22.7-24.6)	0.361
Visceral fat (VF)#	13.5 (10.5-16.25)	12.25 (11.0-14.74)	0.421
52 sting metabolic (RM)#	1388.0 (1341.56-1538.0)	1350.5 (1320.0-1411.0)	0.162
Body mass index (BMI) (kg/m²)#	27.9 (27.1-30.2)	28.65 (27.9-29.5)	0.989

Independent t-test, #Mann-Whitney, *=significant; SD=standard deviation

Table 2: Characteristics of blood chemistry parameters in T2DM patients with obesity and non-DM patients with obesity.

Variable	DM type 2 obesity (n=58)	Non-DM obesity (n=58)	P value
	Median (95% CI)	Median (95% CI)	
Glucose (mg/dl)#	221.5 (157.5-249.0)		<0.001*
Cholesterol (mg/dl) mean±SD	180.6±41.96	180.91±35.62	0.969
Triglycerides (mg/dl) mean±SD	152.55±1.60	113.36±1.50	<0.001*
HDL (mg/dl) mean±SD	26.08±1.37	30.23±.28	0.007*
LDL (mg/dl)#	109.5 (101.0-123.0)	117.0 (107.0-124.0)	0.186
Insulin level#	20.73 (16.07-37.43)	10.47 (8.72-16.4)	0.001*
HOMA β#	71.14±3.52	263.04±2.63	<0.001*
IR HOMA#	11.96 (55 71-16.98)	2.04 (1.85-3.01)	<0.001*

Independent t-test, #Mann-Whitney, *=significant; SD=standard deviation

Table 3: Chi-square test for the characteristics of blood chemistry parameters between the T2DM group with obesity and the non-DM group with obesity.

Variable	DM type 2 obesity n=58		Non-DM obesity n=58		OR (95% CI)	P value
	n	%	n	%		
Insulin						0.032*
High	26	44.8	14	24.1	2.55 (1.155-5.646)	
Normal (2-25 (μIU/ml)	32	55.2	44	75.9	ref	
Glucose						<0.001*
High	47	81.0	0	0.0	236.0 (29.56-5056.92)	
Normal	11	19.0	58	100.0	ref	
Cholesterol						1
High	16	27.6	16	27.6	1.00 (0.443-2.258)	
Normal	42	72.4	42	72.4	ref	
Triglycerides						0.002*
High	31	53.4	14	24.1	3.608 (1.634-7.97)	
Normal	27	46.6	44	75.9	ref	

Continued.

Variable	DM type 2 obesity n=58		Non-DM obesity n=58		OR (95% CI)	P value
	n	%	n	%		
HDL						0.446
Low	20	34.5	25	43.1	0.695 (0.328-1.47)	
Normal	38	65.5	33	56.9	ref	
LDL						0.249
High	40	69.0	33	56.9	1.684 (0.786-3.604)	
Normal <100-129 mg/dl	18	31.0	25	43.1	ref	
HOMA β						0.067
Low	58	100.0	53	91.4	6.56 (0.74-149.2)	
Normal	0	0.0	5	8.6	ref	
HOMA IR >2.7						<0.001*
Low	52	89.7	24	41.4	12.278 (4.546-33.16)	
Normal	6	10.3	34	58.6	ref	

Table 4. Frequency distribution of genotypes (AA, GA, GG) and alleles (A and G) of KCNJ11 genes T2DM obese and non-DM obese patients in ethnic Papuans in Jayapura city.

Variable	DM type 2 obesity n=58		Non DM obesity n=58		OR (95% CI)	P value
	n	%	n	%		
Genotype KCNJ11						1
AA	31	53.4	31	53.4		
GA	26	44.8	26	44.8		
GG	1	1.7	1	1.7		
Genotype KCNJ11						
AA-GA	57	98.3	57	98.3	1.00 (0.061-16.379)	1
GG	1	1.7	1	1.7		
Allele (n=116)						0.881
A	85	73.3	87	75.0	0.914 (0.508-1.645)	
G	31	26.7	29	25.0		

Table 5: Observed value and expected value of KCNJ11 on the research subjects.

Genotype	Score		P value
	Observed value	Expected value	
AA	31	31	1
GA	26	26	
GG	1	1	
Total	58	58	

Table 6: Relationship between blood chemistry parameters with genotype (AA-GA dan AA-GA) KCNJ11 genes with the incidence of T2DM with obesity and non-DM with obesity in ethnic Papuans in Jayapura city.

Variables	DM type 2 dengan obesity n=57		P value	Non DM dengan obesity n=57		P value
	AA (n=31)	GA (n=26)		AA (n=31)	GA (n=26)	
Glucose (mg/dl)#	226.0 (152.5-249.0)	208.5 (155.0-258.0)	0.785	81.0 (77.5-85.0)	82.0 (78.51-88.0)	0.564
Cholesterol (mg/dl) mean\pmSD	185.81 \pm 43.89	174.31 \pm 40.35	0.308	185.55 \pm 39.29	174.85 \pm 31.09	0.256
Triglycerides (mg/dl) mean\pmSD	147.13 \pm 1.56	157.72 \pm 1.64	0.584	110.48 \pm 1.44	118.66 \pm 1.57	0.518
HDL (mg/dl) mean\pmSD	24.98 \pm 1.36	27.69 \pm 1.37	0.224	31.42 \pm 1.28	28.95 \pm 1.28	0.215

Continued.

Variables	DM type 2 dengan obesity n=57		P value	Non DM dengan obesity n=57		P value
	AA (n=31)	GA (n=26)		AA (n=31)	GA (n=26)	
LDL (mg/dl)#	117.0 (108.0-130.0)	93.0 (73.5-110.47)	0.023*	121.0 (110.0-127.0)	112.0 (99.03-129.0)	0.249
Insulin level#	19.46 (9.43-28.28)	31.37 (18.44-51.13)	0.082	9.38 (8.24-19.83)	12.75 (7.49-18.12)	0.898
IR HOMA#	9.36 (5.23-15.83)	13.13 (9.44-26.74)	0.145	1.95 (1.58-3.78)	2.4 (1.52-3.28)	0.835
	AA (n=28)	GA (n=25)		AA (n=23)	GA (n=18)	
HOMA β mean \pm SD	41.81 \pm 2.62	84.03 \pm 2.77	0.013*	196.49 \pm 2.02	161.43 \pm 1.89	0.354

Independent t-test, #Mann-Whitney, *=significant; SD=standard deviation

Table 7: Relationship between blood chemistry parameter and genotypes (AA-GA) of KCNJ11 with the occurrence of T2DM with obesity and non-DM with obesity in ethnic Papuans in Jayapura city.

Variable	Genotype AA			Genotype GA		
	DMT2 obesity median (95% CI) n=31	Non DM obesity median (95% CI) n=31	P value	DMT2 obesity median (95% CI) n=26	Non DM obesity median (95% CI) n=26	P value
Glucose (mg/dl)#	226.0 (152.5-249.0)	81.0 (77.5-85.0)	<0.001*	208.5 (155.0-258.0)	82.0 (78.51-88.0)	<0.001*
Cholesterol (mg/dl) mean \pm SD	185.81 \pm 43.89	185.55 \pm 39.29	0.637	174.31 \pm 40.35	174.85 \pm 31.09	0.927
Triglycerides (mg/dl) mean \pm SD	147.13 \pm 1.56	110.48 \pm 1.44	0.008*	157.72 \pm 1.64	118.66 \pm 1.57	0.035*
HDL (mg/dl) mean \pm SD	24.98 \pm 1.36	31.42 \pm 1.28	0.002*	27.69 \pm 1.37	28.95 \pm 1.28	0.653
LDL (mg/dl)#	117.0 (108.0-130.0)	121.0 (110.0-127.0)	0.888	93.0 (73.5-110.47)	112.0 (99.03-129.0)	0.099
Insulin level (revised)#	19.46 (9.43-28.28)	9.38 (8.24-19.83)	0.153	31.37 (18.44-51.13)	12.75 (7.49-18.12)	0.001*
HOMA β mean \pm SD	57.55 \pm 3.87	282.34 \pm 2.73	<0.001*	93.07 \pm 3.08	235.38 \pm 2.57	0.003*
IR HOMA#	9.36 (5.23-15.83)	1.95 (1.58-3.78)	<0.001*	13.13 (9.44-26.74)	2.4 (1.52-3.28)	<0.001*

Independent t-test, #Mann-Whitney, *=significant; SD=standard deviation

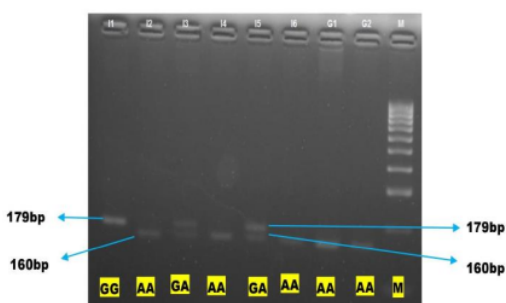


Figure 1. The genotyping results of the KCNJ11 gene E23K polymorphism were determined using the polymerase chain reaction (PCR) - restriction fragment length polymorphism (RFLP) method. The GG genotype was 179bp, the GA genotype was 179 bp, 160 bp, 19 bp, while the AA genotype was 160 bp and 19 bp.

DISCUSSION

This study involved 58 individuals with a history of T2DM with obesity (cases) and 58 samples of non-DM obese individuals (controls) from ethnic Papuans in the city of Jayapura. In this study, two parameters were used, namely anthropometric parameters measured using bioelectrical impedance analysis (BIA) to measure obesity in individuals with T2DM and non-T2DM individuals and blood chemistry parameters to measure profiles of lipid, HOMA IR and HOMA β in T2DM patients with obesity and non-DM patients with obesity.

The results of the study in the examination of anthropometric parameters showed that there was a significant difference between the case group and the control group on diastolic blood pressure variable. Blood pressure is a risk factor for T2DM. The results of this study are also in line with Desmawati research on the correlation of anthropometry measurement with blood pressure and plasma angiotensinogen in 9275 subjects

aged 35-74 years concluded that there is a meaningful relationship between BMI and hypertension ($p < 0.001$). In the results of an examination of blood chemistry parameters, there were significant differences between the case and control groups in the variables of glucose, triglycerides, HDL, insulin levels, HOMA β , and HOMA IR.¹²

Using the cut-off value on the examination of blood chemistry parameters between the case and control groups, the insulin variable showed significant differences: the glucose variable showed statistically significant difference, the triglyceride variable showed a significant difference, and the HOMA variable $IR > 2.7$ showed there was a significant difference. The results of this study are also consistent with research by Sunita et al which showed that fasting blood glucose and plasma insulin levels increased in obese subjects. Obesity is a risk factor for several health conditions such as insulin resistance and metabolic disease. Measurement of blood chemistry parameters for HDL and triglyceride variables were found to be lower in individuals without T2DM compared to individuals with T2DM. This could be due to the dyslipidemia process in patients with T2DM.¹³ According to the consensus of the international diabetes federation defining the syndrome, the method is central obesity accompanied by two of the following symptoms: triglycerides > 150 mg/dl, HDL cholesterol < 40 mg/dl for men, and < 50 mg/dl for women, hypertension, blood pressure $> 130/85$ mmHg and T2DM, or fasting sugar > 100 mg/dl.¹⁴

The description of the frequency distribution of genotypes (AA, GA, GG) and alleles (A and G) of KCNJ11 genes between obese and non-obese T2DM patients among ethnic Papuans in Jayapura city varies. Since the distribution of genotypes is not different between homozygous and heterozygous, then for the AA, GA, and GG genotypes there was no statistically significant difference. Likewise, the frequency of A and G alleles in the case and control groups was statistically not significantly different. The difference in this study with research in several other countries is the research subjects and the number of samples. The subjects of this study were individuals with T2DM with obesity and normal individuals without T2DM with obesity, while research subjects in several countries were healthy normal controls and people with T2DM as cases. Also, the number of samples in studies in several other countries was more than the number of samples in this study. Research conducted by Sunita et al regarding the E23K polymorphism of KCNJ11 in Jogjakarta in 34 individuals with a family history of T2DM and without a family history of T2DM showed that the AA genotype in the family history of T2DM was higher than in individuals without a family history of T2DM. Additionally, the frequency of allele A in the case group was higher than the control group, while for the allele frequency of G in the case group was lower than in the control group.¹⁵

If the results of the research conducted on ethnic Papuans were compared with research on populations of Asia (Japan), Caucasians (Germany), Han (Beijing), Gaza (Palestine), and Java (Yogyakarta), the genotype AA and GA frequencies were higher while the genotype GG was lower. The cause of this difference in frequency is not yet known and may be due to different genetic backgrounds between populations. The Papuan population has genetic similarities with the Asia Pacific population (Melanesoid race) so that if there is a research result from this population, it can be used as comparison data between ethnic groups.

In addition, the Papuan population has a genotype AA frequency both in obese and without obese T2DM sufferers. Because the AA genotype is a risk factor for DM, it can be assumed that the Papuan population is more susceptible to suffering from diabetes although further research is needed to confirm this susceptibility. The results of the chi-square analysis showed that the frequency distribution of the E23K genotype and allele KCNJ11 did not deviate from the Hardy-Weinberg balance, which was not statistically significantly different between the observed value and the expected value ($p = 1$). Thus, the genotypes of the KCNJ11 gene were evenly distributed in the population.

In the description of the relationship between KCNJ11 genotypes (AA-GA and AA-GA) the incidence of T2DM and non-DM with obesity in ethnic Papuans in Jayapura City, for the variable LDL genotype AA - GA statistically showed a meaningful difference in DM2 patients with obesity. While the HOMA β variable the AA-GA genotype showed there was a significant difference in DM2 patients with obesity. Low-Density lipoprotein-cholesterol (LDL-cho) is a lipoprotein that plays a role in the transport of fat fractions, especially cholesterol from the liver to peripheral cells. Dyslipidemia is caused by the accumulation of lipid molecule disorders and IR which is the mechanism of metabolic syndrome that triggers the occurrence of diabetes mellitus. Accumulation of lipid molecules, such as LDL-C, triglycerides (TG), and free fatty acids can impair cell function β and induce IR in peripheral cells. Individuals with increased IR can cause high LDL. It is said that increased LDL-C concentrations are associated with an increased risk of diabetes.¹³

The results of this study are different from research conducted in several populations of other countries such as France, Iran, China, Trinidad, and among the Tunisian population, the Mauritanian population, the Palestinian Gaza subjects, and the Javanese population Sunita et al where individuals carrying the AA genotype have the risk of developing T2DM. Substitution changes in single nucleotide polymorphism GAG \rightarrow AAG causes the substitution of amino acid glutamate to lysine which occurs in the NH2 terminal tail on Kir6.2 and is the ATP binding region. Disruption in one of the binding regions will result in disruption of KATP channel closure so that insulin secretion does not occur which results in

hyperglycemia⁴² can cause T2DM.¹⁵ The KCNJ11 gene plays the most important role in insulin secretion from pancreatic β cells, in addition to stimulation of glucose and voltage-dependent Ca^{2+} ion channels.⁶

In pancreatic β cells, the KCNJ11 gene forms ion channel holes/postures. The gene activity of KCNJ11 is enhanced by phospholipids and acyl CoA and is inhibited by ATP and ADP. The KCNJ11 g³⁹ also plays a role in physiological regulation, glucose homeostasis by regulating insulin secretion from pancreatic β cells.¹⁶

Ezenwaka et al concluded that the presence of GA and AA genotypes in a population in Karabia who had a history of DM did not show a significant relationship with the risk of suffering from T2DM later in life.¹⁷ Ezenwaka et al reported about the polymorphism of p.E23K because KCNJ11 was present in the same number, both in patients with T2DM and healthy individuals (non-DM) so that this polymorphism was not a risk factor for T2DM in the Afro-Caribbean population.¹⁷

Limitations

The sample population of patients with T2DM who are obese and non-DM patients with obesity needed to be increased with the addition of genotype examination of the E23K gene polymorphism and the gene KCNJ11 clinically in the Papuan ethnic group.

CONCLUSION

Based on the results of research on obese patients with T2DM (cases) and non-obese DM patients within the Papuan population in Jayapura city, it can be concluded that: There is no difference in frequency between genotypes and for KCNJ11 gene alleles in the T2DM²⁴ up and non-DM with obesity among ethnic Papuans, there was no statistically significant difference. However, in the analysis of the relationship between the KCNJ11 gene genotype and the incidence of T2DM, the result was statistically significant. The value of the coefficient interval increased in patients with T2DM, which indicated statistically there were significant differences in the variables: glucose, triglycerides, HDL, insulin levels, HOMA β , and HOMA IR.

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