ORIGINAL ARTICLE

Variation of Proconvertase 1 and Resistin Gene as Risk Factor for Type II Diabetes Mellitus in Obesity Papua Population

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ABSTRACT

Introduction: Risk factors for type 2 diabetes mellitus (T2DM) include obesity and some genetic factors. Obesity involves mild chronic inflammation that predisposes cells to insulin resistance. Two genes that influence obesity and insulin resistance are Proconvertase-1 (PC-1) and resistin (RETN). PC-1 affects the activation of hormones that regulate satiety and hunger. Resistin is one of the inflammatory factors that influence the occurrence of insulin resistance. This study aimed to determine the influence of polymorphism in the PC-1 gene rs1044498 (C>A) and resistin gene RETN + 299 G>A rs3745367 on the risk of diabetes in obese Papua population.

Methods: This study involved 58 obese people with T2DM and 58 obese people without DM. We examined the characteristics of blood pressure, lipid profile and insulin resistance by HOMA-IR. The genes examined were PC-1 rs1044498 (C>A) and RETN+ 299 G>A rs3745367 by the PCR-RFLP method. The relationship of gene variations with biochemical parameters was determined with analysis of variance. The results were considered significantly different if P < 0.05.

Results: In this study, parameters of diastolic blood pressure, triglycerides and insulin resistance were higher while high density lipoprotein (HDL) levels were lower and significantly different in the obese with T2DM group compared to the obese only group. The carrier of the A allele in the PC-1 gene rs1044498 was higher in the obese group than the obese with T2DM but not significantly different in biochemical parameters. Carrier of the AA genotype in the RETN gene + 299 G>A rs3745367 had higher triglycerides and HOMA-IR and lower HDL levels significantly different (P<0.05) than other genotypes in the obesity with T2DM group.

Conclusion: PC-1 rs1044498 gene was a risk factor for obesity but not for T2DM, while RETN gene rs3745367 was a risk factor for dyslipidemia and diabetes in obese people in the Papua population.

Keywords: HOMA-IR, Proconvertase-1, Obesity, Resistin, Type 2 Diabetes Mellitus

INTRODUCTION

Obesity increased amounts of non-esterified fatty acids, glycerol, proinflammatory cytokines and other factors are involved in the development of insulin resistance (1). Type 2 diabetes mellitus (T2DM) is a disease characterized by impaired insulin secretion or insulin resistance, or both and the frequency is increasing over time (2). T2DM is influenced by several genes and many biochemical markers including cytokines have been reported to be involved in the incidence of T2DM (3,4). Obesity involves a chronic inflammatory condition that is influenced not only by environmental but also genetic factors. One of the genes that influence obesity is the nucleotide pyrophosphate phosphodiesterase ectoenzyme 1 (ENPP1) or Pro Convertase-1 (PC-1). The risk of diabetes increases significantly with increasing abdominal fat, or in patients with a history of gestational diabetes (5).

Obesity releases inflammatory cytokines including resistin from adipose tissue which is associated with activation of the inflammatory process, and this leads to the inhibition of the insulin secretions through impaired insulin signaling. As a result of this impairment, this disorder may contribute to insulin resistance (6). The PC-1 gene is translated to prohormone convertase 1/3 (PC1/3) as an enzyme, which consists of 14 exons located on chromosome 6 (6q23.2), composed of 6.2 kb. The gene expression is found in the pituitary, brain, and pancreas. The PC1/3 enzyme hydrolyzes a number of hormones such as pro-opiomelanocortin (POMC), prepro-insulin, and proglucagon to ACTH, MSH and active insulin or glucagon, respectively (7). If there is a mutation in this gene, it may be homozygous or heterozygous for causing PC-1 impaired function of an enzyme and has been associated with impaired regulation of hunger
and satiety and plasma glucose levels correlated with an increase in circulating proinsulin/insulin ratio. Activation of preproinsulin is first cleaved by PC1/3 to proinsulin and then further cleavage occurs by PC2 releasing the active form of insulin (8). Disturbances in insulin processing lead to diabetes and obesity. The presence of polymorphism or variation of nucleotides in exon 4 of PC-1 (rs1044498) with changes in the Lysine (K) to Glutamine (Q) (K121Q) have shown an association with the occurrence of T2DM because of increases in the binding affinity to the receptors thereby causing inhibition of the insulin receptors (9). Resistin is a peptide hormone encoded by the resistin gene (RETN), which is located on chromosome 19p13.2 with 4 exons and 3 introns (10). Resistin induces inflammation by stimulating monocytes (11). Resistin binds to the adenylyl cyclase-associated protein 1 (CAP1) receptor in monocytes and converts adenosine triphosphate (ATP) to cAMP, which will activate protein kinase A (PKA), and influence the transcription of NF-B-associated inflammatory cytokines (12), which have an effect on the onset of inflammation. Exposure to resistin over a long time affects the influx of glucose into cells and interferes with the insulin action through its disruption of the tyrosine kinase receptors that induce the expression of glucose transporters (9).

Papua is one of the ethnic groups in the eastern part of Indonesia bordering with the country of Papua New Guinea in the southwestern Pacific, who have different cultural diversity from the western parts of Indonesia. Papua is also considered linguistically diverse in Indonesia, where usually linguistic and cultural diversity is echoed in the genetic structure of the population. The researchers found that groups of people speaking different languages were different genetically from each other (13). Additionally, the living conditions in Papua are different from one decade ago, when the pattern of life was mostly farming and hunting with much physical activity and daily diet consisting of sago and tubers, but now this has all changed. Physical activity has been replaced by machines and the diet involves many energy-rich foods. Prevalence of obesity in Papua Province which was 10.0% in 2013 increased to 20% in 2018 and T2DM prevalence has grown from 0.8% in 2013 to 1.2% in 2018 (14). The increasing prevalence of obesity is indicated by a chronic inflammation condition and increased levels of free fatty acids, which disturb the signals in the influx of glucose into cells, is predicted to increase the prevalence of T2DM. In this study we examined the variations of K121Q PC-1 gene rs1044498 and +299 G>A RETN gene rs 3745367 in obese people with T2DM and obese people without T2DM in the Papuan population.

MATERIALS AND METHODS

Samples
This case–control study involved 116 subjects consisted of 58 obese with T2DM and 58 obese without T2DM who were collected with consecutive random sampling from 7 community health centers in Jayapura, West Papua Province. The two groups were matched with gender and body mass index (BMI). Parameters included T2DM if fasting blood glucose level was >126 mg/dL and obese subjects if BMI > 25 kg/m². Anthropometric and biochemical parameters determined were BMI, systolic and diastolic blood pressure, fasting blood glucose (FBG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides, total cholesterol and fasting insulin were determined by enzymatic methods. Insulin resistance was calculated by homeostatic model assessment for insulin resistance (HOMA –IR) with formula: HOMA-IR index = (fasting insulin (U/ml) x FBG (mmol/l))/22.5. Subject with insulin resistance if HOMA-IR more than 2.5. This research is a follow-up study and part of research conducted by Maay (15). Inclusion and exclusion criteria were as follows: for cases, they were probands willing to be a research subject by signing the informed consent form; Diagnosed with T2DM, based on the criteria of the American Diabetic Association (ADA, 2014)(16) with fasting blood glucose > 126 mg/dL (7.0 mmol/L) or plasma glucose levels > 200 mg/dL (11.1 mmol/L); obese with BMI ≥ 25Kg/m² and Ethnic Papua who has lived in Papua for 3 generations or above. Controls were: obese subjects with BMI ≥ 25 kg/m² and normoglucone levels. The exclusion criteria were: patients with insulin therapy and pregnant women.

Genotyping of K121Q (C>A) PC-1 and +299 G>A RETN genes
Genotyping of PC-1 gene (C>A) (rs1044498) was done with PCR-RFLP. Primers for amplification of DNA: F-5’ GCAATTCTGTGTTCACTTTGGA-3’ and R-5’ GACGCACCTGACCTTGACACA-3’. The result of PCR was 207 base pair and then digested by Avali endonuclease enzyme (17). Products of RFLP were electrophoresed with 2% agarose gel with Florosave staining gel. Digested products were: 207 for C allele and +299 G>A RETN gene was amplified with the following primers: F-5’ GAAGGATCCCGAGGTTGTCG 3’ and R-5’ GTGCAGACCAACGTTCCA 3’. PCR was done as follows: 5 minutes at 95°C for denaturation, 59°C 1 min for pre-annealing, 72°C 2 min for elongation, then repeat 35 cycles with 30 s at 95°C, 30 s at 59°C and 1 min 15 s at 72°C, and the last for elongation at 72°C for 10 min. Product of PCR was 373 base pair (bp) then digested by endonuclease AluI enzyme. Products of RFLP then underwent electrophoresis with 2% agarose gel and stained with Florosave (18). Products of RFLP for G allele were: 243, 55, 52 and 23 bp and for A allele were 158, 85 55, 52 and 23 bp. Because the 55 and 52 bp were near to each other and 23 bp was too small, other
than the RFLP products for G and A allele in this site were same so we saw the RFLP products as follows: GG genotype were 243 and 55 bp; GA genotype were 243, 158, 85 and 55 bp; and AA genotype were 158, 85 and 55 bp.

Ethics approval of this research was granted from the Ethics Committee of the Health Polytechnic of Jayapura with Amendment number: 068/KEPK-J/IX/2021

Statistical analysis
Data obtained from the two groups: obesity with T2DM and obesity without DM were analyzed with SPSS 22 (IBM Corp., Armonk, NY) and comparison of the two groups used T-tests if data were homogeneous and presented as mean with standard deviation (SD). For non-homogeneous data, the parameters were compared with Mann-Whitney tests and presented with minimum-maximum (min-max) data. Risk factors of PC-1 and RETN genes in obese subject compared to obese subjects with T2DM were calculated with odds ratio (OR). Risk of genotype related to biochemical parameters were calculated with ANOVA. P<0.05 was considered significantly different.

RESULTS
This study consisted of 58 obese with T2DM and 58 obese subjects without T2DM from the Papua population with the characteristics of subjects shown in Table I.

This study found significant differences in diastolic blood pressure, glucose, triglycerides, HDL, insulin level and HOMA-IR index in the obese subjects with T2DM compared to the obese only group in the Papua population.

Genotype of AA in PC-1 C>A (rs1044498) gene was not found in any of the subjects. Results showed that the carrier of A gene and A allele were more significant risk factors of obesity than DM. Variations of the RETN +299G>A gene were not found to be a risk factor for diabetes in obese subjects from Papua population (Figure 1).

Table II shows there were no correlations of PC-1 rs1044498 genotype with biochemical parameters in obese subjects with DM nor obese subjects without DM.

Table III shows in the variation of RETN +299G>A gene, there were the highest triglyceride levels, HOMA-IR index and lowest HDL levels in AA genotype in T2DM with obesity patients compared with the other genotypes (P<0.05). In the obese without T2DM group, this genotype did not significantly differ in all of the biochemical characteristics. These results indicate that the variation of RETN +299G>A genotype in obese person with DM plays a role in causing dyslipidemia, especially high levels of triglycerides and low levels of HDL. In addition, the variation in this genotype causes insulin resistance as indicated by higher HOMA-IR in the AA genotype than other genotypes. Insulin levels were also highest in the carriers of the AA genotype compared to other genotypes (GA and GG), but were not significantly different.

DISCUSSION
This study found, higher diastolic blood pressure, dyslipidemia especially higher triglyceride and lower HDL levels. Results also revealed higher insulin levels and HOMA-IR index in obese subjects with DM compares with the obese without DM group. PC-1 C>A K121Q rs 1044498 genotype was found to be a risk factor for obesity more than diabetes, but this genotype was not correlated with biochemical parameters. RETN

Table I: Characteristic anthropometric of obesity with T2DM and obesity without T2DM Papua Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obesity with T2DM (n=58)</th>
<th>Obesity non T2DM (n=58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.843</td>
</tr>
<tr>
<td>Man (%)</td>
<td>20 (34.5)</td>
<td>18 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Women (%)</td>
<td>38 (65.5)</td>
<td>40 (69.0)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>55.0±10.08</td>
<td>51.26±10.33</td>
<td>0.049</td>
</tr>
<tr>
<td>Body weight (Kg) #</td>
<td>69.2 (66.0-72.7)</td>
<td>68.25 (65.0-72.5)</td>
<td>0.533</td>
</tr>
<tr>
<td>Height (cm) #</td>
<td>150.0 (145.0-156.0)</td>
<td>157.0 (154.0-157.0)</td>
<td>0.498</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg) #</td>
<td>120.0 (115.0-128.0)</td>
<td>113.0 (110.0-120.0)</td>
<td>0.060</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg) #</td>
<td>85.0 (80.01-90.0)</td>
<td>80.0 (78.0-81.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Glucose (mg/dL) #</td>
<td>221.5 (157.5-249.0)</td>
<td>80.69±11.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>180.6±35.62</td>
<td>180.91±35.62</td>
<td>0.969</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>152.5±1.60</td>
<td>113.36±1.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>26.08±1.37</td>
<td>30.23±28</td>
<td>0.007</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>109.5 (101.0-123.0)</td>
<td>117.0 (107.0-124.0)</td>
<td>0.186</td>
</tr>
<tr>
<td>Insulin level</td>
<td>20.73 (16.07-37.43)</td>
<td>10.47 (8.72-16.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>11.96 (7.71-16.98)</td>
<td>2.04 (1.85-3.01)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

# = Mann-Whitney

Figure 1: Frequency of PC-1 C>A and RETN G>A genes as risk factor for T2DM in obese Papua population
Table II: Correlation of PC-1 C>A rs1044498 gene with biochemical characteristic in obesity with DM and obesity without DM in Papua Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>T2DM with Obesity N=58</th>
<th>P Value</th>
<th>Obese non T2DM N=58</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC (n=51)</td>
<td>CA (n=7)</td>
<td>CC (n=40)</td>
<td>CA (n=18)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>222 (163.5,246.5)</td>
<td>217 (131-316)</td>
<td>80 (78.85)</td>
<td>0.953</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>183.7±42.59</td>
<td>158±30.51</td>
<td>176.98±33.56</td>
<td>0.245</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>152.67±1.61</td>
<td>151.59±1.48</td>
<td>114.56±1.50</td>
<td>0.669</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>25.86±1.37</td>
<td>27.94±1.41</td>
<td>29.67±1.28</td>
<td>0.407</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>711 (104-126)</td>
<td>74 (66.51-128.97)</td>
<td>117.5 (107-124)</td>
<td>0.475</td>
</tr>
<tr>
<td>Insulin Level</td>
<td>20.54 (16.29-40.7)</td>
<td>21.08 (10.63-61.13)</td>
<td>10.47 (7.58-15.67)</td>
<td>0.94</td>
</tr>
<tr>
<td>IR Homa</td>
<td>12.24 (7.07-19.03)</td>
<td>9.703 (5.12-34.33)</td>
<td>2.04 (1.65-3.01)</td>
<td>0.987</td>
</tr>
</tbody>
</table>

Table III: Correlation of RETN +299G>A genotype with biochemical characteristic in obesity with DM and obesity without DM in Papua Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>T2DM with Obesity N=58</th>
<th>P Value</th>
<th>Obese non T2DM N=58</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG (n=12)</td>
<td>CA (n=35)</td>
<td>AA (n=11)</td>
<td>GG (n=13)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>176.5 (129.0,272.2)</td>
<td>226.0 (155.0,244.0)</td>
<td>117.0 (199.0,355.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>181.3±57.23</td>
<td>184.86±39.96</td>
<td>166.27±26.70</td>
<td>0.447</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>157.92±1.34</td>
<td>144.77±1.64</td>
<td>173.52±1.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>26.5±3.13</td>
<td>27.92±1.37</td>
<td>20.83±1.25</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>114.0 (64.34,154.0)</td>
<td>111.0 (91.12-129.0)</td>
<td>101.0 (71.0-117.0)</td>
<td>0.477</td>
</tr>
<tr>
<td>Insulin Level</td>
<td>17.65 (11.56-34.03)</td>
<td>20.92 (12.94-40.84)</td>
<td>41.12 (14.91-90.26)</td>
<td>0.285</td>
</tr>
<tr>
<td>IR Homa</td>
<td>7.51 (4.61-26.74)</td>
<td>11.47 (6.69-15.82)</td>
<td>17.38 (13.66-72.87)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

+299 G>A genotype in this population was not a risk factor for T2DM in obese patients, but carriers of AA genotype had the highest levels of triglycerides and HOMA-IR index with the lowest HDL level compared to GG and AG genotypes. Additionally, the carriers of the variation of G>A RETN +299 gene have an increased risk of dyslipidemia and insulin resistance.

The PC-1 gene encodes the Proconvertase-1 enzyme that converts POMC to MSH which acts on MC4R which will give the effect of fullness and inhibit the desire to eat. If there is a mutation in the PC-1 gene, it will interfere with the feeling of satiety so that the desire to eat is not controlled which eventually causes obesity. An in vitro study found that the variation of the PC-1 gene (rs1044498) in exon 4, with changes of Lysine by Glutamine (K121Q), causes increased binding affinity to the receptors leading to inhibition of receptor function in regulating hunger and satiety.

Results of our PC-1 K121Q gene are consistent with studies in Swedish, Danish and British populations that also found this gene variation was not associated with T2DM (19-21). In a European study, examining variation in the PC-1 Q121 gene showed that this gene was associated with high BMI in a recessive model (QQ compared to KK + KQ) (21). In the result of our study examining the K121Q variation of the PC-1 gene, no QQ genotype was found, similar to our previous study in a population of Java, West Indonesia, and this gene variation also showed that the KQ genotype was a risk factor for obesity (22). Research in another Javanese population with T2DM and control groups showed that this genetic variation is associated with the decrease of insulin sensitivity or increase of insulin resistance (23). Mutations in this gene cause impaired function of the PC-1 enzyme and was associated with obesity because it affects the processing of several hormones that regulate satiety and hunger functions (24). Another in vitro study indicated that the presence of the PC-1 gene polymorphism in exon 4, with the conversion of the Lysine by Glutamine (K121Q), causes increased binding affinity to the receptors causing inhibition of receptor function in regulating hunger and satiety (25).

The study conducted by Zhao (26) examining the association between PC-1 with T2DM and obesity showed that K121Q rs1044498 ENPP1 gene showed no significant association with T2DM, obesity or metabolic syndrome. These results were supported by a meta-analysis in the Chinese population which showed no negative association between the K121Q variation of the PC-1 gene with susceptibility to T2DM or obesity. In Asian Indian populations, the frequency of K121Q PC-1 was higher than in Europeans (27) and highest in African-Americans (28). It appears that 121Q of the PC-1 gene may contribute to insulin resistance in different populations.

Different results in the polymorphism of the K121Q PC-1 gene were seen in a meta-analysis study in Caucasian and Asian populations which showed a
significant relationship between \textit{PC-1} gene encoding the Q amino acid compared to the K of subjects with obesity and T2DM (26). The meta-analysis research by McAteer et al. (29) revealed that the Q121 variant of \textit{PC-1} gene increases the risk of T2DM with a recessive inheritance model in Caucasians. A meta-analysis by Li (30) demonstrated that carriers of the Q121 variant of the \textit{PC-1} gene may be predisposed to T2DM risk. Studies in some population of African-American, Hispanic and non-Hispanic populations showed the higher the frequency of Q121 \textit{PC-1} gene, and there were higher numbers of patients T2DM. Logistics regression analysis revealed significant correlations between \textit{PC-1} genotypes by age, and BMI (31).

Our study about the G>A variation of the \textit{RETN} +299 gene showed that the polymorphism was not significantly different between the obese subjects with T2DM and the obese without T2DM group. However, subjects with a variation of G>A \textit{RETN} +299 gene have a risk of dyslipidemia especially increased triglyceride levels, lower HDL-C and increased insulin resistance showed by HOMA-IR. The same result was found among the populations in the western areas of Indonesia, where this genotype was a significant risk factor for insulin resistance in the obese group compared to the controls (32). Resistin induces inflammation by stimulating monocytes. Resistin binds to the adenylyl cyclase-associated protein 1 receptor in monocytes, influencing the conversion of ATP to cAMP, activating protein kinase A, and influencing the transcription of NFκB-associated inflammatory cytokines which have an effect on inflammation (33). Chronic exposure to resistin interferes with insulin action through its disruption of the receptor tyrosine kinase that induces expression of glucose transporter-1 and 4 and affects influx of glucose into cells (34). Research on the mRNA genes involved in glucose metabolism and insulin signaling pathways showed that resistin decreased insulin receptor substrate -2 mRNA and stimulated the expression of suppressors of cytokine signaling, which causes glucose intolerance by inhibiting insulin signal transduction pathways (35) as a pathogenesis of resistin in decreasing insulin sensitivity. Another study analyzed the effect of resistin and found the decreasing of insulin sensitivity was due to interference in insulin signaling in insulin target tissues (36,37). Resistin interferes with endothelin-1 levels by inducing proliferation and migration of human endothelial cells, increasing the release of vascular endothelial growth factor receptors (VEGFRs) and matrix metalloproteinases (MMPs) expression (38).

In a North Indian study on the \textit{RETN} gene at SNP +299 G>A rs3745367 analyzing its association with T2DM risk showed that carriers of the GA + AA genotype had higher insulin and HOMA-IR activity than carriers of the GG genotype (39). Researchers also showed that the \textit{RETN} gene polymorphism was correlated with resistin levels, while the A genotype had higher level of resistin in the diabetes subjects compared to the controls (40). The frequency of AA genotype and A allele were higher in the T2DM group compared to the control group with either the additive, the recessive, or the dominant models. The same results were also found in the Caucasian population (20), in Iraq (41), as well as a meta-analysis study (31), in Egypt (42) and in Thailand (43). Researchers (44) further found that serum resistin levels in T2DM patients were positively correlated with Waist/Hip ratio, C-reactive protein, insulin resistance, and lipid profile, but negatively correlated with HDL-C. Pathogenesis of the polymorphism in the intron, +299 (G>A), is thought to affect gene expression and may contribute to increased resistin level as an inflammatory marker in subjects with DM (43). This parameter can be used as a biomarker for the severity of DM (45).

One study conducted by Al Hilali showed there were statistically significant differences in fasting blood glucose, serum resistin, fasting insulin, insulin resistance as HOMA-IR and % HbA1C in the AA compared to the GA and GG genotypes of the T2DM group (41) and these results matched other studies (46) because the expression may be cis-regulated, meaning the presence of variations close to or in the \textit{RETN} gene may affect the increase of mRNA transcription (47). Some associations were found between the \textit{RETN} +299 (G/A) gene variation and insulin sensitivity in the T2DM group, and the HOMA index as an indicator of insulin resistance was significantly higher in subjects with AA and AA+GA genotypes compared to GG when compared to the controls.

Another research showed different results in a Japanese population, indicating there was no significant correlation between the \textit{RETN} gene variation at SNP rs3745367 as a risk factor for diabetes (48), as well as in Han Chinese patients (49). The investigators who studied the BMI (< or 27.5 kg/m2 and > 27.5 kg/m2) stated that insulin function and resistin levels did not differ. They concluded that resistin did not have a strong relationship with adiposity, the action of insulin and metabolic syndrome in humans (5). Studies in the USA and Malaysia showed that +299 (G>A) \textit{RETN} gene variation was not associated with parameters of diabetes that were fasting blood glucose, insulin level, HOMA index & HbA1c in AA, and GA+GG subgroups compared with control subjects (50).

Some limitations of this research were the limited number of samples, so that in examining the variation in the \textit{PC-1} gene, although it has a high risk of causing obesity, this gene’s variation does not show any differences in biochemical characteristics, especially in carbohydrate metabolism, with Obesity classification based on the Asian group (BMI>25). This grouping of obesity in terms of health risks may be sufficient, but if it is associated with genetic variation as a risk factor for changes in biochemical characteristics, it needs to be reviewed.
also did not examine environmental factors associated with obesity and diabetes. Environmental factors may modify genes, especially diet composition and physical activity that affect gene expression. Variations between populations with different gene pools may influence gene imbalances and gene variations which can confer different risks for diseases. Further research about these genes’ polymorphisms can be used by geneticists and clinicians to investigate the molecular basis for the pathogenesis of a specific disease or syndrome. Additionally, the presence of certain genetic factors as risk factors for disease can be used as a basis for individual pharmacogenetic and nutrigenetic managements.

CONCLUSION

In this study we can conclude that variation in PC-1 genotype is more likely to increase the risk for obesity than T2DM, but it is not associated with biochemical parameters. The RETN gene variation is associated with impaired insulin resistance and lipid profile disorder in the Papua population.

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