RETN GENE SINGLE NUCLEOTIDE POLYMORPHISM PROFILE ON TRIGLYCERIDE-GLUCOSE INDEX AS INSULIN RESISTANCE PROXY AMONG COHORT POPULATION OF NON-COMMUNICABLE DISEASES IN BOGOR

by Frans Final

Submission date: 30-May-2022 09:21PM (UTC+0700)
Submission ID: 1847235947
File name: Frans_Final.docx (173.2K)
Word count: 4878
Character count: 26806

ISSN 0216-3438 (Print). ISSN 2621-1122 (Online)

Jurnal Profesi Medika : Jurnal Kedokteran dan Kesehatan

RETN GENE SINGLE NUCLEOTIDE POLYMORPHISM PROFILE ON TRIGLYCERIDE-GLUCOSE INDEX AS INSULIN RESISTANCE PROXY AMONG COHORT POPULATION OF NON-COMMUNICABLE DISEASES IN BOGOR

Frans Dany[1]*, Uly Alfi Nikmah[1], Ratih Rinendyaputri[1], Fitrah Ernawati[1], Dewi Kristanti[2], Fifi Retiaty[1]

[1] Badan Riset Inovasi Nasional (BRIN)

[2] Badan Kebijakan Pembangunan Kesehatan (BKPK), Kementerian Kesehatan RI

*Correspondence e-mail: fransdany1@gmail.com

ABSTRACT

Genetic factors such as single nucleotide polymorphisms (SNPs) are thought to contribute to the increasing incidence of diabetes mellitus (DM) through insulin resistance. SNPs in the RETN (resistin) gene encoding the resistin protein have been reported to play a role in causing abnormalities in blood glucose and lipid metabolism. Still, studies related to this have rarely been explored in cohort population models. This study aimed to evaluate the relationship of resistin gene SNPs to the trend of the triglyceride-glucose index (TyG) as a proxy for insulin resistance. The data were obtained from the results of the biomedical laboratory examination among participants of a cohort study in the Kebon Kalapa subdistrict, Bogor, every odd year period between 2015-2021 and from RETN genotyping (rs3745367). The generalized linear model (GLM) repeated measurement technique was used with the TyG index value as the dependent variable. The results of the GLM analysis showed that although there was a significant difference in the trend of the TyG index between the observation periods [F(2,87, 1671,1)=41,10, p-value <0.001], that's not the case for RETN gene SNP [F(5,73, 1671,1) = 1.09, p-value = 0.367]. However, the multivariate test results suggested the association of these SNPs with age and DM status [F(4, 583)=2.48, p-value = 0.043]. In conclusion, RETN gene SNPs may require interaction with other factors or genes to induce insulin resistance or act by indirect glucose–fatty acid metabolic cycle mechanisms.

Keywords: Cohort; Diabetes Melitus; Resistin; Single Nucleotide Polymorphism; Triglyceride-Glucose index

INTRODUCTION

An increasing trend of type 2 diabetes mellitus (DM) is observed across the globe, notably in developing countries, and puts a lot of economic burden on a country's healthcare system.[1,2] Besides urbanization that leads to lifestyle changes, genetics is thought to complicate its control.[3] One such determinant is *single nucleotide polymorphisms* or SNPs.[4] SNPs are changes in one nucleotide base in a specific gene area, which may cause unexpected consequences. As the concept of personalized medicine is being promoted, the place of genetic risk factors such as SNPs would play a vital role in the management of non-communicable diseases (NCDs) like DM.[5]

One such SNP is that located in the RETN gene. RETN encodes a protein, resistin, and may function in regulating lipid and glucose metabolism, so any abnormalities in its expression are hypothesized to be related to insulin resistance.[6] Insulin resistance is one hallmark of DM and other metabolic disorders such as obesity and metabolic syndrome.[7] Hence, its measurement is essential when we would like to estimate someone's risk of having diabetes in the future.[8] Several methods have been proposed and performed to measure insulin resistance levels, namely via HEC and HOMA-IR. However, its wide use is hampered by its invasiveness, impracticality, and high cost.[9] Another way is by calculating the triglyceride-glucose (TyG) index, which has been carried out in healthcare facilities because it's more convenient for the patients and cheaper. Moreover, it has a good correlation with HOMA-IR as reference.[10–12]

Given that insulin resistance dynamics may be affected by SNPs, a study on them and their influence on varying degrees of insulin resistance are desperately needed. Yet, the results of such are greatly determined by population size and need to be observed in a timely manner to identify any significant changes.[13] Even though some research on SNPs was already done in several countries, its availability using a cohort-based approach, particularly in Asian countries, including Indonesia, is still limited.[14] Therefore, this study aimed to evaluate the association of RETN SNPs with the trend of the TyG index as a proxy for insulin resistance in our cohort-based population model for NCDs in Indonesia. We genuinely hope that the results of this investigation may add valuable insights into the importance of developing genetic risk factor screening for NCDs on a larger scale within our society.

MATERIALS AND METHODS

Study Design and Ethical Approval

This study is observational and experimental using valuable biological material (VBM) taken from cohort study participants for NCD risk factors from 2015 to 2021, conducted by Badan Litbangkes Ministry of Health, Indonesia. VBM in the form of the *buffy coat* was first extracted in 2015. This procedure obtained Ethical Approval from Komisi Etik Badan Litbangkes (The Ethical Committee of NIHRD) number LB.02.01/5.2/KE.229/2015 and lastly in 2021 with the reference number LB.02.01/2/KE.169/2021. Blood sample collection was done every big follow-up period in an odd year (2015, 2017, 2019, and 2021) after participants fully explained their rights, risks, and benefits to our research team and signed written informed consent. Respondents also had the right to participate in a certain period or drop out voluntarily.

1.1 Sample and Location

Purposive sampling were those who agreed to join in the Cohort Study of Risk Factors for NCDs carried out by the Ministry of Health, Indonesia, and aged 25-80 years old. The data collection took place in the Kebon Kalapa subdistrict, Bogor City, West Java Province, Indonesia.

1.2 Genotyping

Whole blood samples collected were added with Ficoll solution in a 1:1 volume ratio and centrifuged at 1500 rpm for 15 minutes to isolate its greyish buffy coat part. Buffy coats were later processed in the genetic material extraction step using

Qiagen® kit to get the DNA that was later used for RETN SNP (rs3745367) genotyping. Genotyping was performed using TaqMan® Assay kit in real-time PCR (7500 Fast Real-Time PCR System), which was already connected with Applied Biosystem software in a personal computer for further genotype data analysis.

1.3 Biomedical Parameter Test

A whole blood sample was centrifuged at 1500 rpm for 10 minutes to separate its serum from other compartments. Blood glucose and lipid profile level were measured using an automatic enzymatic-based approach to clinical chemistry. The results were validated by a clinical pathologist who monitored the lab examiner throughout this study. Biomedical data collection was still done normally in 2019 prior to the official announcement of the COVID-19 pandemic by the Indonesian Government. Meanwhile, data collection in 2021 was carried out following strict safety protocol and was already granted permission under close supervision by the COVID-19 Task Force of local authorities. Fasting plasma glucose (FPG) and triglyceride level were obtained among those who already went fasting for 12-14 hours prior to the first venous blood collection. The calculation of the TyG index follows the formula proposed by Simental *et al.*[15]:

TyG index = Ln [{FPG level (mg/dl) X triglyceride level (mg/dl)} / 2]

1.4 Inclusion, Exclusion Criteria, and Data Management

Secondary data on FPG and triglycerides were taken from the study period in 2015, 2017, 2019, and 2021 which were later merged with RETN SNP genotyping results besides supporting sociodemographic information on participant's age and gender. Inclusion criteria encompassed all respondents who followed the cohort study and took samples for genotyping. Pregnant women, those who did not participate in cohort *follow-up* continuously, or any missing data were excluded from our final analysis.

1.5 Data Analysis

Merged data were analyzed descriptively and inferentially. The relationship of the TyG index according to the observation period and other variables was evaluated using the generalized linear model (GLM) repeated measure technique. If the assumption of *sphericity* is not met, then the Greenhouse-Geisser correction will be selected to determine the *p-value*.[16] Multivariate analysis for within-subject effects was done to assess the interaction between variables. Statistical significance is determined at *p-value* <0,05, and effect size is estimated by using *partial eta square* (η_p^2). Most analyses were performed using SPSS software version 15.0 and Microsoft Excel 2016.

ISSN 0216-3438 (Print). ISSN 2621-1122 (Online)

RESULT

Table 1. Characteristics of participants in the cohort study for NCD risk factors who managed to participate continuously from 2015 until 2021 (n=618)

Categorical variables	**n**	**%**
Age (*baseline*)		
<45 years old	249	40.3
≥45 years old	369	59.7
Gender		
Male	189	30.6
Female	429	69.4
RETN SNP rs3745367		
GG allele (*Wild-type*)	71	11.5
AG allele (Hetero)	262	42.4
AA allele (Variant)	285	46.1
Numerical variables	**Mean ± SD**	**Standard of Error**
Age (*baseline* 2015)	47.13 ± 9.49	0.382
FPG (*baseline* 2015)	86.67 ± 44.77	0.974
Triglyceride (*baseline* 2015)	118.24 ± 60.91	2.55
TyG index (*baseline* 2015)	8.41 ± 0.52	0.02

As shown in Table 1, most participants were older than 45 years old and women since the 2015 baseline period. The RETN rs3745367 genotype demonstrated that those with variant allele AA accounted for the biggest proportion and were almost half of the total respondents taking part in our final data analysis. While Table 2 displays the results of GLM on averaged TyG index concerning observation period and other determinants. It also shows the contrast between 2 consecutive periods by considering the interaction of the time variable, namely the period with other determinants. Statistically, there was no significant association of RETN gene SNPs relative to time. However, there were generally significant differences, especially until the 3rd observation period in 2017 and in the 2nd period when we consider the DM status of the respondents. However, different things were obtained from the multivariate within-subject effects analysis (Table 3), which found a significant relationship between the SNPs of the RETN gene concerning the period of observation and interaction with the variables of age and DM status.

ISSN 0216-3438 (Print). ISSN 2621-1122 (Online)

Table 2. Results of the generalized linear model (GLM) repeated measure analysis on averaged TyG index in relation to an observation period

Within-Subject Effects	**Correction**	***Sum of Square***	**df**	***Mean Square***	**F**	***p-value***	**ηp²**
Period	Greenhouse-Geisser	14.804	2.87	5.165	41.10	**< 0.001**	**0.066**
Period * RETN gene SNP	Greenhouse-Geisser	0.783	5.73	0.137	1.09	0.367	0.004
Period * DM status	Greenhouse-Geisser	2.863	5.73	0.499	3.97	**< 0.001**	**0.013**
Period * Gender	Greenhouse-Geisser	1.050	2.87	0.366	2.92	**0.035**	**0.005**
Period * Age group	Greenhouse-Geisser	1.061	2.87	0.370	2.94	**0.034**	**0.005**
Error(Period)	Greenhouse-Geisser	209.973	1671.1	0.126			
Within-Subject Contrasts	**Contrast between periods**	***Sum of Square***	**df**	***Mean Square***	**F**	***p-value***	**ηp²**
Period	Period 1 vs. 2	13.783	1	13.783	56.13	**< 0.001**	**0.088**
	Period 2 vs. 3	1.056	1	1.056	5.08	**0.025**	**0.009**
	Period 3 vs. 4	0.021	1	0.021	0.11	0.744	0.000
Period * RETN gene SNP	Period 1 vs. 2	0.167	2	0.084	0.34	0.711	0.001
	Period 2 vs. 3	0.535	2	0.267	1.29	0.277	0.004
	Period 3 vs. 4	0.114	2	0.057	0.28	0.753	0.001
Period * DM status	Period 1 vs. 2	3.516	2	1.758	7.16	**< 0.001**	**0.024**
	Period 2 vs. 3	0.748	2	0.374	1.80	0.166	0.006
	Period 3 vs. 4	0.412	2	0.206	1.03	0.358	0.004
Period * Gender	Period 1 vs. 2	0.117	1	0.117	0.48	0.491	0.001
	Period 2 vs. 3	0.266	1	0.266	1.28	0.258	0.002
	Period 3 vs. 4	0.243	1	0.243	1.21	0.272	0.002
Period * Age group	Period 1 vs. 2	0.289	1	0.289	1.18	0.279	0.002
	Period 2 vs. 3	0.528	1	0.528	2.54	0.112	0.004
	Period 3 vs. 4	0.006	1	0.006	0.03	0.860	< 0.001
Error(Period)	Period 1 vs. 2	143.162	583	0.246			
	Period 2 vs. 3	121.151	583	0.208			
	Period 3 vs. 4	116.966	583	0.201			

DISCUSSION

Determination of the reference allele is still determined based on information from the National Center Biotechnology Information (NCBI) database from various sources. In the RETN case, the reference allele (wild-type) is the GG allele, while the change from G to A is considered a variant.[17] The large proportion of variant alleles in Table 1 is also close to the minor allele frequency (MAF) allele A in the Qatari population and some genome mapping research databases such as 1000 Genomes and HapMap.[18] Even so, the proportion of SNP alleles for the RETN gene in Table 1 cannot be directly concluded for all Indonesian populations. Considering the process of sorting samples that have gone through the selection of inclusion and exclusion criteria, the proportion of SNP

alleles here did not represent the true proportion. In addition, the SNP database information on the NCBI is still dominated by data on the Caucasian race population and not the Southeast Asian population race.[19]

Table 3. Multivariate analysis of within-subjects on TyG index concerning an observation period

Variable interaction	Test type	Test value	F	Hypothesis df	Error df	*p-value*	ηp²
Period * RETN gene SNP * Age group	Pillai's Trace	0.005	0.49	6	1164	0.819	0.002
	Wilks' Lambda	0.995	0.49	6	1162	0.819	0.003
	Hotelling's Trace	0.005	0.49	6	1160	0.820	0.003
	Roy's Largest Root	0.005	0.94	3	582	0.421	0.005
Period * RETN gene SNP * Gender	Pillai's Trace	0.013	1.28	6	1164	0.265	0.007
	Wilks' Lambda	0.987	1.27	6	1162	0.266	0.007
	Hotelling's Trace	0.013	1.27	6	1160	0.267	0.007
	Roy's Largest Root	0.007	1.33	3	582	0.262	0.007
Period * RETN gene SNP * DM status	Pillai's Trace	0.018	0.90	12	1749	0.548	0.006
	Wilks' Lambda	0.982	0.90	12	1537.47	0.549	0.006
	Hotelling's Trace	0.019	0.90	12	1739	0.551	0.006
	Roy's Largest Root	0.012	1.70	4	583	0.149	0.012
Period * RETN gene SNP * DM status * Age group	Pillai's Trace	0.027	1.34	12	1749	0.190	0.009
	Wilks' Lambda	0.973	1.34	12	1537.47	0.191	0.009
	Hotelling's Trace	0.028	1.34	12	1739	0.191	0.009
	Roy's Largest Root	0.017	2.48	4	583	**0.043**	**0.017**
Period * RETN gene SNP * DM status * Age group	Pillai's Trace	0.017	0.83	12	1749	0.621	0.006
	Wilks' Lambda	0.983	0.83	12	1537.47	0.622	0.006
	Hotelling's Trace	0.017	0.83	12	1739	0.624	0.006
	Roy's Largest Root	0.009	1.30	4	583	0.267	0.009
Period * RETN gene SNP * Gender * Age group	Pillai's Trace	0.005	0.52	6	1164	0.795	0.003
	Wilks' Lambda	0.995	0.52	6	1162	0.796	0.003
	Hotelling's Trace	0.005	0.52	6	1160	0.796	0.003
	Roy's Largest Root	0.004	0.87	3	582	0.455	0.004

On the other hand, the mean triglyceride-glucose index (TyG) as a proxy for insulin resistance at the baseline stage was higher than the average reported in several studies in other countries and indicates that insulin resistance is already present.[12,20–22] This can happen because most of the respondents who participated in the PTM cohort study in Bogor had entered the age category at risk of developing DM.[23] Increasing the age of a person is thought to have an impact on decreasing glucose and lipid metabolism in the body in addition to increasing pancreatic beta-cell apoptosis and impaired oxidative stress which results in reduced insulin sensitivity and glucose uptake in peripheral tissues.[24]

The overall trend of increasing the TyG index is significantly different from period 1 in 2015 to period 4 in 2021 (Table 2) with an

intermediate effect size if we look at the partial eta square value (η_p^2) that is 0.066.[25] In addition to age, a significant relationship between the TyG index was also found in the interaction between the observation period and gender and DM status but not with the RETN gene polymorphism. Meanwhile, one significant relationship (Table 3) was detected when we used Roy's Largest Root test, which is suitable for use when the variance is heterogeneous with an unbalanced number of samples between groups.[26]

The contribution of the RETN gene polymorphism is shown again in Figure 1, and Figure 2, where respondents with the AA variant allele generally have a higher TyG index mean value than individuals with the reference allele. In Figure 1A, individuals with the AA variant allele show an increasing trend in the TyG index from the baseline period to 2021. However, based on DM status (Figure 1B-1D), the pattern shows differences, especially in the 3rd and 4th periods. This can be caused, among others, by changes in a person's lifestyle and other factors that cause fluctuations in insulin resistance.[27] The interesting thing in Figure 1 is that normoglycemic respondents with the GG reference allele showed an increasing trend in the TyG index at the end of the observation. This information indicates that other factors influence the increase in the index, such as unhealthy diet patterns and lack of physical activity in these individuals.[28,29]

Meanwhile, the trend pattern of the TyG index is also different between men and women (Figures 2E and 2F). The increase in the pattern was also dominantly observed between the baseline period and 2017, while the pattern of the increase in the TyG index in respondents with the reference allele was also shown in the 3rd period, especially in female respondents. Various factors, such as lack of knowledge about indications of DM or metabolic syndrome, can result in a high TyG index during this period as they began to pay attention to their health, especially during the COVID-19 pandemic.[30] However, both male and female respondents with the variant allele showed a higher TyG index value at the end of the observation than the heterozygous and wild-type allele categories.

Different relationship characteristics were observed by age group (Figs. 2G and 2H). Individuals aged <45 years also showed an increasing trend of the TyG index until the 3rd period, with a close distance between the variant allele group and the heterozygous allele group. On the other hand, for those aged 45 years and over, there is a trend line distance between the three allele groups except for the 2019 observations. However, the increase in the TyG index is relatively consistent in this group of individuals with allele variants. This again confirms the interaction of RETN polymorphism with age category, which posed an increased risk of insulin resistance.

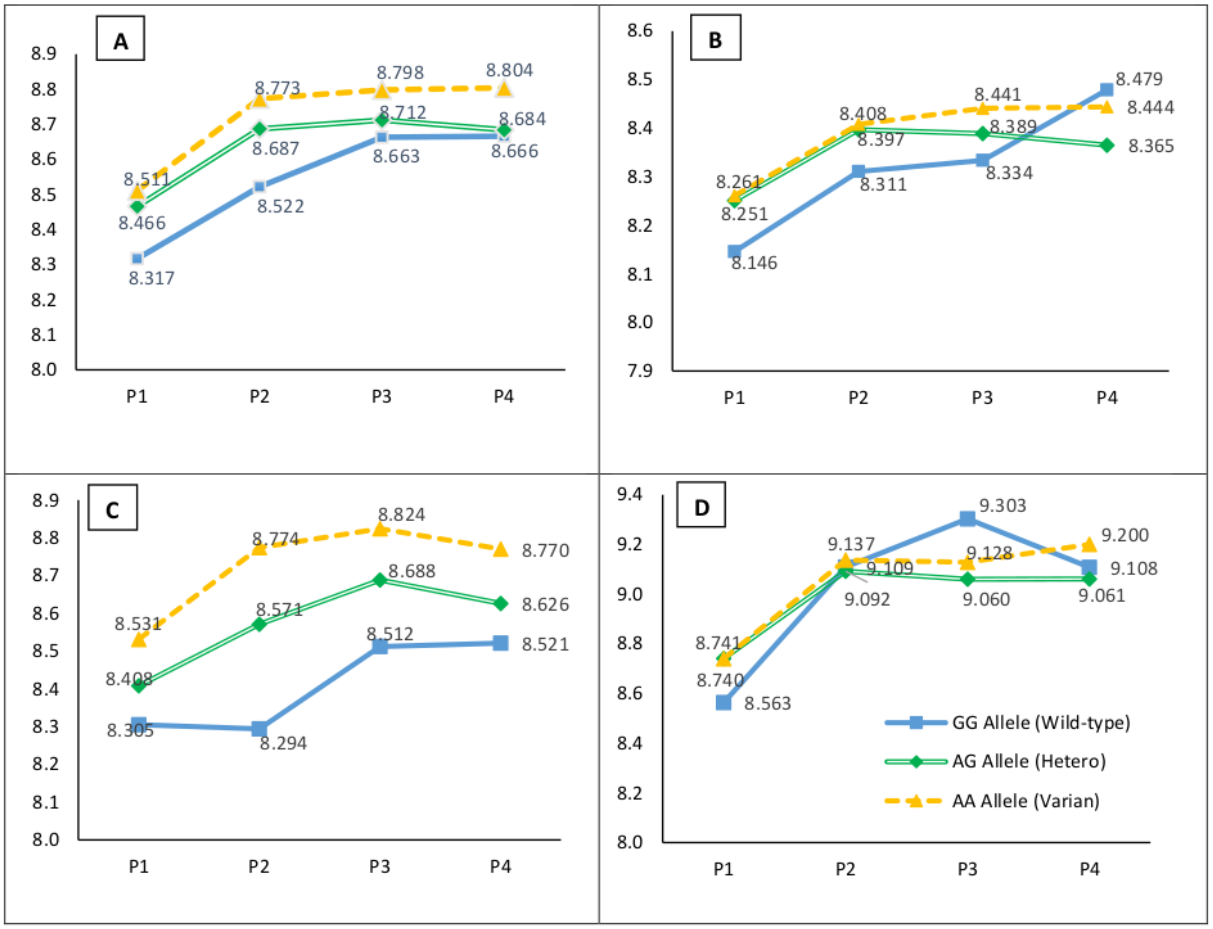

Figure 1. Trend profile of average TyG index over four observation periods (P1-P4) according to 3 (three) allele categories for RETN SNP and status of blood glucose level. A) TyG index trend in general by allele categories; B) TyG index trend in normoglycemic individuals; C) TyG index trend in those with prediabetes and D) TyG index trend among people with diabetes (type 2 DM).

From the information presented in the table and figure above, the potential contribution of the RETN gene polymorphism to insulin resistance, as reflected in the TyG index proxy parameter, is still found but not statistically significant. We need to consider the mean value of the respondent's TyG index since the baseline period is already quite high. From the results of multivariate analysis, there are indications that the RETN gene polymorphism does not work alone and may involve interactions with other factors or even genes in causing insulin resistance.[3,31,32] The RETN gene is a gene whose function is to regulate glucose homeostasis and adipogenesis. In humans, the resistin protein expressed by this gene competes with lipopolysaccharides when it binds to toll-like receptor 4 (TLR4) mononuclear cells so that it is thought to mediate cellular inflammatory processes in various diseases, including diabetes mellitus.[33]

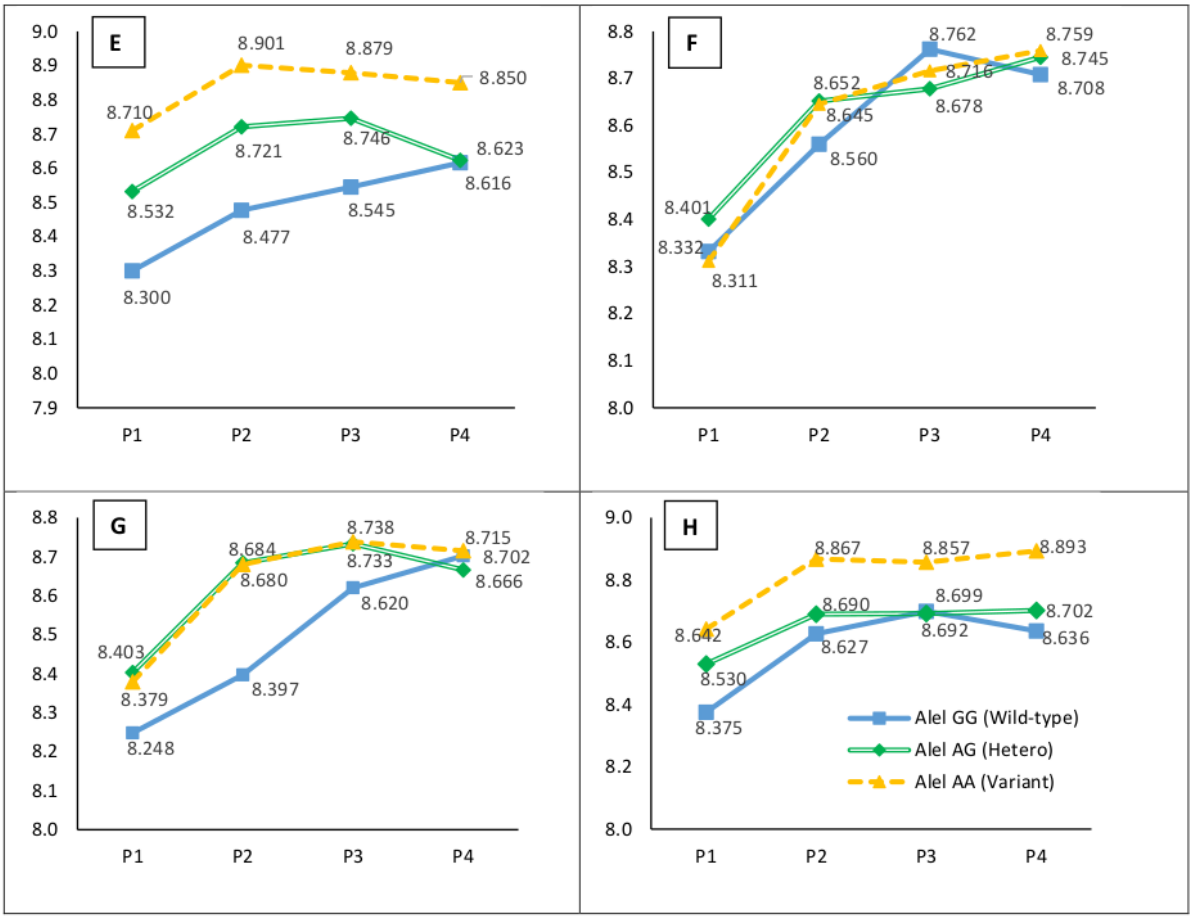

Figure 2. Trend profile of averaged TyG index over four observation periods (P1-P4) according to gender and age group. E) TyG index trend among men; F) TyG index trend among women; G) TyG index trend in those aged <45 years old and H) TyG index trend in those aged ≥45 years old.

Resistin protein is also thought to contribute to insulin receptor damage in peripheral tissues resulting in impaired glucose uptake.[34] Abnormalities of glucose and lipid metabolism accompanied by cellular inflammatory processes led to the thought of the interaction of genetic factors on the process of insulin resistance, and several studies reported that variations in fasting blood glucose levels were related to genetic factors.[35] Given the many factors that can influence this resistance, it is possible that some SNPs work through certain pathways other than the glucose and fatty acid metabolism cycle.[7,24,36]

The location of the RETN gene SNP in the intron area at position 299 was chosen because it was found to be associated with the risk of developing DM in Asian populations in several studies, but the analysis carried out in these overseas studies still implemented a cross-sectional design.[6,37] This study focused

on identifying associations between these SNPs and trends in insulin resistance over the four observation periods. The location of these SNPs in the RETN gene area may contribute to a non-significant relationship in this study, considering that there are several regions of RETN SNPs whose impact on the phenotype has not been explored. However, the aspect of substantive significance needs to be considered in addition to the statistical significance of the results of the GLM analysis in this study. The high mean TyG index has the potential risk of microvascular and macrovascular complications caused by insulin resistance.[38]

In addition to the limitations of the continuous sample following the cohort consistently, the results of this analysis also have not considered other variables that can affect insulin resistance without adding to the complexity of interpreting the results. It is also worth noting that a representative SNP database used specifically for the Indonesian population is not yet available, so further studies are needed regarding mapping specific SNPs to a particular outcome through a genome sequencing approach.[39] Subanalysis of the influence of SNPs or in-depth bioinformatic analysis of interactions between SNPs on a phenotype under certain conditions can also be carried out in future studies to obtain a more detailed understanding of the mechanism of SNPs in the emergence of pathological processes.[40] The results of such a study are expected to provide insight into the importance of genetic risk factor screening in alignment with the concept of personalized medicine in disease management.

CONCLUSION

This study suggested that although there was no statistical significance between RETN SNP rs3745367 with TyG index trend as insulin resistance proxy, a hint of its influence was noted from the results of multivariate analysis, which was corroborated by the TyG index trend plots over observation periods. RETN SNP rs3745367 (+299 G>A) was not dominant and might need interaction with other genes and risk factors or perhaps work in other indirect mechanisms of the glucose-fatty acid metabolism cycle.

REFERENCES

1. Misra A, Gopalan H, Jayawardena R, Hills AP, Soares M, Reza-Albarrán AA, et al. diabetes in developing countries. J Diabetes. 2019;11(7):522–39.
2. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep [Internet]. 2020;10(1):1–11. Available from: https://doi.org/10.1038/s41598-020-71908-9
3. Mambiya M, Shang M, Wang Y, Li Q, Liu S, Yang L, et al. The Play of Genes and Non-genetic Factors on Type 2 Diabetes. Front Public Heal. 2019;7(349):1-8.
4. Sun W, Yao S, Tang J, Liu S, Chen J, Deng D, et al. Integrative analysis of super enhancer SNPs for type 2 diabetes. PLoS One. 2018;13(1):1–16.
5. Liao WL, Tsai FJ. Personalized medicine in type 2 diabetes. Biomed. 2014;4(2):1–8.
6. Vardarlı AT, Harman E, Çetintaş VB, Kayıkçıoğlu M, Vardarlı E, Zengi A, et al. Polymorphisms of lipid metabolism enzyme-coding genes in patients with diabetic dyslipidemia. Anatol J Cardiol. 2017;17(4):313–21.
7. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. J Clin Invest.

2016;126(1):12–22.
8. Sharma VR, Matta ST, Haymond MW, Chung ST. Measuring Insulin Resistance in Humans. Horm Res Paediatr. 2021;93(11–12):577–88.
9. Buchanan TA, Watanabe RM, Xiang AH. Limitations in surrogate measures of insulin resistance. J Clin Endocrinol Metab. 2010;95(11):4874–6.
10. Lee DY, Lee ES, Kim JH, Park SE, Park C, Oh K, et al. Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes : A 4-Year Retrospective Longitudinal Study. 2016;1–14.
11. Adriana S, Mancillas-adame L, Gonz V, Alejandro D, Solis RC, Alvarez-villalobos NA, et al. Diagnostic Accuracy of the Triglyceride and Glucose Index for Insulin Resistance : A Systematic Review. 2020;2020(4678526):1-7. doi: 10.1155/2020/4678526
12. Aman M, Resnawita D, Rasyid H, Kasim H, Bakri S, Umar H, et al. The concordance of triglyceride glucose index (TyG index) and homeostatic model assessment for insulin resistance (Homa-IR) in non-diabetic subjects of adult Indonesian males. Clin Epidemiol Glob Heal [Internet]. 2021;9:227–30. Available from: https://doi.org/10.1016/j.cegh.2020.09.003
13. Costanza MC, Beer-Borst S, James RW, Gaspoz JM, Morabia A. Consistency between cross-sectional and longitudinal SNP: Blood lipid associations. Eur J Epidemiol. 2012;27(2):131–8.
14. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segrè A V., Steinthorsdottir V, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet. 2012;44(9):981–90.
15. Simental-Mendía LE, Guerrero-Romero F. The correct formula for the triglycerides and glucose index. Eur J Pediatr. 2020;179(7):1171.
16. Armstrong RA. Recommendations for analysis of repeated-measures designs: testing and correcting for sphericity and use of manova and mixed model analysis. Ophthalmic Physiol Opt. 2017;37(5):585-593.
17. Chung CM, Lin TH, Chen JW, Leu HB, Yin WH, Ho HY, Sheu SH, Tsai WC, Chen JH, Lin SJ PW. Common quantitative trait locus downstream of RETN gene identified by genome-wide association study is associated with risk of type 2 diabetes mellitus in Han Chinese: a Mendelian randomization effect. Diabetes Metab Res Rev [Internet]. 2014;30(3):232–40. Available from: http://www.heartcenter.org.tw/ch/wp-content/uploads/2015/03/Referred-paper-No.-75.pdf
18. National Center for Biotechnology Information. rs3745367 RefSNP Report - dbSNP - NCBI [Internet]. [cited 2022 Feb 10]. Available from: https://www.ncbi.nlm.nih.gov/snp/rs3745367
19. Huang T, Shu Y, Cai YD. Genetic differences among ethnic groups. BMC Genomics [Internet]. 2015;16(1):1–10. Available from: http://dx.doi.org/10.1186/s12864-015-2328-0
20. Salazar J, Bermúdez V, Calvo M, Olivar LC, Luzardo E, Navarro C, et al. Optimal cutoff for the evaluation of insulin resistance through triglyceride-glucose index: A cross-sectional study in a Venezuelan population. F1000Research. 2017;6(1337):1-15.
21. Moon S, Park JS, Ahn Y. The Cut-off Values of Triglycerides and Glucose Index for Metabolic Syndrome in

American and Korean Adolescents. J Korean Med Sci. 2017;32(3):427–33.
22. Endukuru CK, Gaur GS, Yerrabelli D, Sahoo J, Vairappan B. Cut-off values and clinical utility of surrogate markers for insulin resistance and beta-cell function to identify metabolic syndrome and its components among southern indian adults. J Obes Metab Syndr. 2021;29(4):281–91.
23. Perkumpulan Endokrinologi Indonesia (PERKENI). Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia 2020. (2020). PB PERKENI. PERKENI [Internet]. 2020;46:11-13. Available from: https://pbperkeni.or.id/wp-content/uploads/2021/11/22-10-21-Website-Pedoman-Pengelolaan-dan-Pencegahan-DMT2-Ebook.pdf
24. Salmon AB. Oxidative stress in the etiology of age-associated decline in glucose metabolism. Longev Heal. 2012;1(1):1–8.
25. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. Front Psychol. 2013;4(NOV):1–12.
26. Kale HE, Tekindal MA. Comparison of Test Statistics of Nonnormal and Unbalanced Samples for Multivariate Analysis of Variance in terms of Type-I Error Rates. 2019;2019(2173638):1-8. doi: 10.1155/2019/2173638.
27. Galaviz KI, Narayan KMV, Lobelo F, Weber MB. Lifestyle and the Prevention of Type 2 Diabetes: A Status Report. Am J Lifestyle Med. 2018;12(1):4–20.
28. Sacks M. F, Carey J. V, Anderson A. M. C, Miller III R. E, Copeland T, Charleston J, et al. Effects of High vs Low Glycemic Index of Dietary Carbohydrate on Cardiovascular Disease Risk Factors and Insulin Sensitivity. JAMA - J Am Med Assoc [Internet]. 2014;312(23):2531–41. Available from: https://pubmed.ncbi.nlm.nih.gov/25514303/
29. Kim KS, Kim SJ, Kim S, Choi D, Ju YJ, Park E. Association of self-reported sedentary time with insulin resistance among Korean adults without diabetes mellitus : a cross- sectional study. 2018;18(1335):1–8.
30. Tiwari A, Kumar D, Ansari MS, Chaubey SK, Gupta NR, Agarwal V, et al. Impact of lockdown on self-care management among patients with type 2 Diabetes Mellitus residing in Lucknow city, India – A cross-sectional study. Clin Epidemiol Glob Heal [Internet]. 2021;10(100703):1-6. Available from: https://doi.org/10.1016/j.cegh.2021.100703
31. Lau CH, Muniandy S. Lack of evidence for intermolecular epistatic interactions between adiponectin and resistin gene polymorphisms in Malaysian male subjects. Genet Mol Biol. 2012;35(1):38–44.
32. Kumar D, Lee B, Puan KJ, Lee W, Luis BS, Yusof N, et al. Resistin expression in human monocytes is controlled by two linked promoter SNPs mediating NFKB p50/p50 binding and C-methylation. Sci Rep. 2019;9(1):1–16.
33. Tarkowski A, Bjersing J, Shestakov A, Bokarewa MI. Resistin competes with lipopolysaccharide for binding to toll-like receptor 4. J Cell Mol Med. 2010;14(6b):1419–31.
34. Gerrits AJ, Gitz E, Koekman CA, Visseren FL, van Haeften TW, Akkerman JWN. Induction of insulin resistance by the adipokines resistin, leptin, plasminogen activator inhibitor-1 and retinol binding protein 4 in human megakaryocytes. Haematologica. 2012;97(8):1149–57.
35. Wang T, Huang T, Zheng Y, Rood J, Bray GA, Sacks FM QL. Genetic

variation of fasting glucose and changes in glycemia in response to 2-year weight-loss diet intervention: the POUNDS Lost trial. Int J Obes [Internet]. 2016;40(7):1164–1169. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4935586/pdf/nihms-759150.pdf

36. Samuel VT, Shulman GI. Mechanisms for insulin resistance: Common threads and missing links. Cell [Internet]. 2012;148(5):852–871. Available from: http://dx.doi.org/10.1016/j.cell.2012.02.017
37. Kumar V, Singh J, Bala K, Singh J. Association of resistin (rs3745367) and urotensin II (rs228648 and rs2890565) gene polymorphisms with risk of type 2 diabetes mellitus in Indian population. Mol Biol Rep [Internet]. 2020;47(12):9489–97. Available from: https://doi.org/10.1007/s11033-020-05991-6
38. Lee SB, Ahn CW, Lee BK, Kang S, Nam JS, You JH, et al. Association between triglyceride glucose index and arterial stiffness in Korean adults. Cardiovasc Diabetol [Internet]. 2018;17(1):11–6. Available from: https://doi.org/10.1186/s12933-018-0692-1
39. Zook JM, Chapman B, Wang J, Mittelman D, Hofmann O, Hide W, et al. Integrating human sequence data sets provides a resource of benchmark SNP and indel genotype calls. Nat Biotechnol. 2014;32(3):246–51.
40. Elkhattabi L, Morjane I, Charoute H, Amghar S, Bouafi H, Elkarhat Z, et al. In silico analysis of coding/noncoding SNPs of human RETN gene and characterization of their impact on resistin stability and structure. J Diabetes Res. 2019;2019(4951627):1-9. doi: 10.1155/2019/4951627.

RETN GENE SINGLE NUCLEOTIDE POLYMORPHISM PROFILE ON TRIGLYCERIDE-GLUCOSE INDEX AS INSULIN RESISTANCE PROXY AMONG COHORT POPULATION OF NON-COMMUNICABLE DISEASES IN BOGOR

ORIGINALITY REPORT

14%	13%	10%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Universitas Indonesia Student Paper	3%
2	ejournal.upnvj.ac.id Internet Source	2%
3	d-scholarship.pitt.edu Internet Source	2%
4	www.ymj.or.kr Internet Source	1%
5	www.frontiersin.org Internet Source	1%
6	www.researchsquare.com Internet Source	<1%
7	cardiab.biomedcentral.com Internet Source	<1%
8	digitalcommons.njit.edu Internet Source	<1%

9	hdl.handle.net Internet Source	<1 %
10	docplayer.net Internet Source	<1 %
11	Ki-Woong Nam, Min K Kang, Han-Yeong Jeong, Tae J Kim et al. "Triglyceride-glucose index is associated with early neurological deterioration in single subcortical infarction: Early prognosis in single subcortical infarctions", International Journal of Stroke, 2021 Publication	<1 %
12	www.jove.com Internet Source	<1 %
13	link.springer.com Internet Source	<1 %
14	worldwidescience.org Internet Source	<1 %
15	www.biorxiv.org Internet Source	<1 %
16	Frans Dany, Rita Marleta Dewi, Dwi Hapsari Tjandrarini, Julianty Pradono et al. "Urban-rural distinction of potential determinants for prediabetes in Indonesian population aged ≥15 years: a cross-sectional analysis of Indonesian Basic Health Research 2018	<1 %

	among normoglycemic and prediabetic individuals", BMC Public Health, 2020 Publication	
17	bmccancer.biomedcentral.com Internet Source	<1 %
18	mafiadoc.com Internet Source	<1 %
19	oamjms.eu Internet Source	<1 %
20	www.gssrr.org Internet Source	<1 %
21	www.repository.cam.ac.uk Internet Source	<1 %
22	www.sfn.org Internet Source	<1 %
23	1library.net Internet Source	<1 %
24	Metabolic Syndrome, 2016. Publication	<1 %
25	eprints.sinus.ac.id Internet Source	<1 %
26	kjim.org Internet Source	<1 %
27	theses.lib.polyu.edu.hk Internet Source	<1 %

28	www.science.gov Internet Source	<1%
29	www.slideshare.net Internet Source	<1%
30	Xiaoteng Ma, Lisha Dong, Qiaoyu Shao, Yujing Cheng, Sai Lv, Yan Sun, Hua Shen, Zhijian Wang, Yujie Zhou, Xiaoli Liu. "Triglyceride glucose index for predicting cardiovascular outcomes after percutaneous coronary intervention in patients with type 2 diabetes mellitus and acute coronary syndrome", Cardiovascular Diabetology, 2020 Publication	<1%
31	fomin zhang, yingyi zhang, zhigang guo, hua yang, min ren, xiaomeng xing, hongliang cong. "The association of triglyceride and glucose index, triglyceride to high density lipoprotein cholesterol ratio with prehypertension and hypertension in normoglycemic subjects: a large cross-sectional population study ", Research Square, 2021 Publication	<1%
32	www.ncbi.nlm.nih.gov Internet Source	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		