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Rizal Fahly[1], Fabiola M.S. Adam[1], Haerani Rasyid[1], Andi Makbul Aman[1], Syakib Bakri[1], Idar Mappangara[1], Andi Alfian Zainuddin[2]

[1]Department of Internal Medicine, Medical Faculty, Hasanuddin University, Makassar, Indonesia

[2]Department of Biostatistics, Public Health Faculty, Hasanuddin University, Makassar, Indonesia

Relationship between TG/HDL-C Ratio and TyG Index with Chronic Inflammation in People with Prediabetes: A Cross-Sectional Study

ABSTRACT

Objective: Prediabetes is an insulin resistance (IR) condition. The triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) ratio and triglyceride-glucose (TyG) index were associated with prediabetes and IR condition which are related to cardiovascular disease (CVD). High sensitive-CRP (hs-CRP) is a marker of inflammation that is closely related to CVD. The aim of this study is to determine the correlation between TG/HDL-C ratio and TyG index with hs-CRP as a marker of chronic inflammation in impaired fasting glucose (IFG).

Material and methods: An observational study with a cross-sectional approach involved 92 people with prediabetes in Makassar City, Indonesia, in February 2022. Research subjects were participants of Makassar Lipid and Diabetes Study aged 18–70 years who met inclusion criteria. Triglyceride, HDL-C, fasting plasma glucose (FPG), and hs-CRP were examined. Level of hs-CRP > 3–10 mg/L is a high risk of CVD. Prediabetes is defined by fasting plasma glucose of 100–125 mg/dL. Statistical analysis was performed using Kruskal-Wallis and Chi-Square tests.

Results: The mean TG/HDL-C ratio was 4.88, the mean TyG index was 4.92, and the mean hs-CRP level was 4.53 ± 2.91 mg/L. There was no statistically significant relationship between TG/HDL-C ratio and high hs-CRP levels in people with prediabetes (p = 0.45). There was no statistically significant relationship between the TyG index and high hs-CRP levels in people with prediabetes (p = 1.00).

Conclusions: There is no statistically significant relationship between TG/HDL-C ratio or TyG index and hs-CRP in people with prediabetes defined by IFG. (Clin Diabetol 2022; 11; 5: 321–325)

Keywords: TG/HDL-C ratio, TyG index, hs-CRP, prediabetes

Address for correspondence:
Prof. Dr. Haerani Rasyid, MD
Department of Internal Medicine
Hasanuddin University, Faculty of Medicine
Perintis Kemerdekaan Km 10, Tamalanrea, Makassar 90245,
South Sulawesi, Indonesia
phone: +6281310087900
e-mail: haeraniabdurasyid@yahoo.com
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Introduction

Prediabetes is a condition that refers to the intermediate stage of dysglycemia where glucose levels are in the range between normoglycemia and diabetes. Prediabetes is used to identify individuals who are at risk of diabetes and associated high risk of cardiometabolic events [1]. In people with prediabetes, insulin resistance (IR) has been found where there is an increase in inflammatory factors such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other proinflammatory cytokines [2, 3]. Inflammation is thought to be the key

mechanism in the pathogenesis of atherosclerosis, from the formation and progression of the plaque to its rupture, and stent restenosis. Vascular inflammatory changes can hardly be evaluated using imaging methods, so testing inflammatory biomarkers in the blood is important. Currently, high sensitive-CRP (hs-CRP) is one of the markers of chronic inflammation that is closely related to the risk of cardiovascular disease (CVD) [4].

The ratio of serum triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) is known as the plasma atherogenic index and is one of the risk factors for CVD and metabolic syndrome [5]. The simultaneous use of TG and HDL-C in a ratio is more useful than isolated lipid values as it more closely reflects the complex interactions of lipoprotein metabolism and can better predict plasma atherogenicity [6]. Studies show that hypertriglyceridemia and low HDL-C levels are the two major metabolic disorders associated with IR. A study by Yeh W.C. et al. [7] showed that a significantly increased TG/HDL-C ratio was closely associated with insulin resistance and could be used as an indicator of IR.

An additional marker associated with IR is triglyceride-glucose (TyG) index [5]. The TyG index calculated by the formula [Ln (fasting TG level (mg/dL) × fasting plasma glucose (mg/dL)/2)]. A high TyG index is significantly associated with a higher risk of developing type 2 diabetes [8]. The TyG index has been shown to be a simple, efficient, and clinically useful surrogate marker for IR. Two recent studies showed that the TyG index was closely correlated with the homeostasis model assessment of insulin resistance index (HOMA-IR). Several other studies reported that the TyG index value was superior in estimating IR compared to HOMA-IR. Elevated hs-CRP carries a much higher risk of developing IR. The study by Kim R.G. et al. [9] reported that high levels of hs-CRP caused systemic inflammation independent of IR as measured by the TyG index.

This study aimed to determine the correlation between TG/HDL-C ratio and TyG index with hs-CRP as a marker of chronic inflammation in people with prediabetes in February 2020 at Makassar City, Indonesia. In addition, we also explored the relationship between TG/HDL-C ratio and TyG index with hs-CRP levels in assessing the risk of cardiovascular events.

Materials and methods

Research Design

This was an observational study with a cross-sectional approach in Makassar City, Indonesia.

Research subjects

Research subjects were taken from Makassar Lipid and Diabetes Study who were included in the inclusion criteria. Research subjects who met the inclusion criteria were age range 18–70 years old, fasting plasma glucose (FPG) 100–125 mg/dL, and exclusion criteria were type 1 diabetes, type 2 diabetes, other types of diabetes, hs-CRP > 10 mg/L.

Table 1. Subject Characteristics

Variable	Male (n = 42) Mean ± SD	Female (n = 50) Mean ± SD	Total (n = 92) Mean ± SD
Age [years]	51.4 ± 7.9	51.9 ± 8.9	51.7 ± 8.4
FPG [mg/dL]	108.2 ± 7.5	108.9 ± 7.7	108.6 ± 7.5
HDL-C [mg/dL]	47.8 ± 11.9	45.1 ± 13.2	46.3 ± 12.6
TG [mg/dL]	194.7 ± 104.1	193.6 ± 107.4	194.1 ± 105.3
TyG index	4.92 ± 0.26	4.92 ± 0.26	4.92 ± 0.26
TG/HDL-C ratio	4.58 ± 3.40	5.13 ± 4.35	4.88 ± 3.93
hs-CRP [mg/L]	5.06 ± 2.91	4.09 ± 2.87	4.53 ± 2.91

FPG — fasting blood glucose; HDL-C — high-density lipoprotein cholesterol; hs-CRP — high sensitive C-reactive protein; SD — standard deviation; TG — triglyceride; TyG — triglyceride glucose

Data collection

Sampling was done by simple random sampling. All blood samples were taken after 12-hour fasting by a phlebotomist and were examined in the Hasanuddin University Hospital Research Laboratory. High density lipoprotein cholesterol and TG used homogenous enzymatic colorimetric assay, plasma glucose by enzymatic hexokinase, and hs-CRP levels were measured using the Diagnostics Biochem Canada Inc kit, by the ELISA method.

Data analysis

Data analysis was performed using SPSS version 22. The statistical tests used were Kruskal-Wallis and Chi-Square tests. The results were considered significant if the p-value < 0.05.

Ethical clearance

This study protocol was approved by the Health Research Ethics Commission of Hasanuddin University, Medical Faculty, following the ethical recommendations with approval letter number: 60/UN4.6.4.5.31/PP36/2022. This publication was prepared without any external source of funding.

Results

The study was conducted during the period February 2022. During that period, 92 samples were obtained that met the inclusion criteria, consisting of 42 males and 50 females. The subject characteristics are shown

Table 2. The Relationship between TG/HDL Ratio and TyG Index with hs-CRP Levels in People with Prediabetes

	n	hs-CRP Median (Min–Max)	*p-value
TG/HDL-C ratio			
< 2.83	30	5.19 (0.40–9.76)	0.38
2.83–4.59	31	4.05 (0.36–9.68)	
> 4.59	31	3.12 (0.42–10.0)	
TyG index			
< 4.80	28	5.0 (0.36–9.70)	0.58
4.80–5.01	33	3.42 (0.42–9.76)	
> 5.01	31	4.0 (0.42–10.0)	

*Kruskal-Wallis test
HDL-C — high-density lipoprotein cholesterol; hs-CRP — high sensitive C-reactive protein; TG — triglyceride; TyG — triglyceride glucose

in Table 1. The age of the subjects was between 32–69 years with an average age of 51.7 years. The TG/HDL-C ratio ranges from 0.56 to 21.16 with a mean of 4.88. The TyG index has a range of 4.11–5.59 with an average of 4.92. The mean hs-CRP level of the subjects was 4.53 ± 2.91. Table 2 shows the relationship between TG/HDL-C ratio and hs-CRP levels in people with prediabetes. The value of the TG/HDL-C ratio was divided into 3 tertiles. Tertiles 1 and 2 are considered low, tertile 3 is high. The number of tertile 1 subjects (< 2.83) were 30 subjects, tertile 2 (2.83–4.59) were 31 subjects, and tertile 3 (> 4.59) were 31 subjects. There was no statistically significant relationship between TG/HDL-C ratio and hs-CRP levels (p = 0.38). Table 3 also shows the relationship between the TyG index and hs-CRP levels in people with prediabetes. The TyG index value is divided into 3 tertiles. Tertiles 1 and 2 are considered low, tertile 3 is high. The number of tertile 1 subjects (< 4.80) were 28 subjects, tertile 2 (4.80–5.01) were 31 subjects, and tertile 3 (> 5.01) were 31 subjects. There was no statistically significant relationship between the TyG index and hs-CRP levels (p = 0.58).

The relationship between the TG/HDL-C ratio and hs-CRP levels in assessing the risk of cardiovascular events is shown in table 3. The hs-CRP levels > 3–10 mg/L represent chronic inflammation with an increased risk of cardiovascular events compared to hs-CRP values ≤ 3. The TG/HDL-C ratio was divided into high risk and low risk and the hs-CRP value was divided into 2, low ≤ 3 mg/L and high > 3–10 mg/L. Chi-Square test showed that there was no significant relationship between TG/HDL-C ratio with hs-CRP in assessing the risk of cardiovascular events (p = 0.45). Table 4 shows the relationship between the TyG index and hs-CRP levels in assessing the risk of cardiovascular events. The TyG index was divided into high risk and low risk and the hs-CRP value was divided into 2, low ≤ 3 mg/L and high > 3–10 mg/L. Chi-Square test showed that there was no significant relationship between the ratio of TyG index and hs-CRP in assessing the risk of cardiovascular events (p = 1.00).

Table 3. Relationship of TG/HDL-C Ratio and TyG Index with hs-CRP in Assessing the Risk of Cardiovascular Events

	hs-CRP		*p-value
	≤ 3 mg/L (low)	> 3–10 mg/L (high)	
TG/HDL-C ratio			
≤ 4.59 (low)	23	38	0.45
> 4.59 (high)	15	16	
TyG index			
≤ 5.01 (low)	25	36	1.00
> 5.01 (high)	13	18	

HDL-C — high-density lipoprotein cholesterol; hs-CRP — high sensitive C-reactive protein; TG — triglyceride; TyG — triglyceride glucose.

Table 4. The Relationship between the Ratio of TG/HDL-C with High hs-CRP in Prediabetes Subjects Aged < 40 Years and Aged ≥ 40 Years

	hs-CRP		p-value
	≤ 3 mg/L (low)	> 3–10 mg/L (high)	
Aged < 40 years			
TG/HDL-C ratio			
≤ 6.65 (low)	3	3	1.00
> 6.65 (high)	2	1	
TyG index			
≤ 5.16 (low)	3	3	1.00
> 5.16 (high)	2	1	
Aged ≥ 40 years			
TG/HDL-C ratio			
≤ 4.58 (low)	20	36	0.40
> 4.58 (high)	13	14	
TyG index			
≤ 5.02 (low)	22	34	1.00
> 5.02 (high)	11	16	

HDL-C — high-density lipoprotein cholesterol; hs-CRP — high sensitive C-reactive protein; TG — triglyceride; TyG — triglyceride glucose

Discussion

There were 92 study subjects who met the study criteria. In this study, the mean value of HDL-C in male patients with prediabetes was 47.8 mg/dL and in female patients with prediabetes was 45.1 mg/dL, with the

overall mean value of 46.3 mg/dL. The mean level of TG in this study was 194.1 mg/dL. This result is higher than HDL-C and TG levels in people with prediabetes in a study conducted by Bhowmik B. et al. [10] and Kansal S. et al. [11].

The mean level of hs-CRP in the subjects of this study was 4.53 mg/L and this level was categorized as high (> 3–10 mg/L). These results are in line with the research conducted by Chakarova N. et al. [12] who found that people with prediabetes showed significant differences in all parameters analyzed, namely total cholesterol levels, LDL-C, TG, free fatty acids (FFA), and hs-CRP were significantly higher while HDL-C levels were significantly lower than in normal subjects, with a mean hs-CRP value in patients with IFG of 4.4 mg/L. High sensitive C-reactive protein is an inflammatory protein that represents a subclinical inflammatory state in prediabetes and its levels can be of predictive value in the development of atherosclerosis and diabetes. High levels of hs-CRP were found in patients with IFG and impaired glucose tolerance (IGT) and were significantly higher when compared to subjects whose glucose tolerance was normal and significantly lower than for patients with newly diagnosed diabetes. Insulin resistance is the main determinant of hs-CRP concentration.

The results of this study showed that there was no significant relationship between the TG/HDL-C ratio and hs-CRP levels as a marker of chronic inflammation in people with prediabetes ($p = 0.38$). This result is different from the research conducted by Ramanujapura D. et al. [13], in witch total cholesterol, TG, VLDL, and low-density lipoprotein (LDL) showed a positive correlation while HDL-C showed a negative correlation with IR and hs-CRP. The ratio of TG/HDL-C and HOMA-IR increased significantly in the CHD group. High sensitivity CRP has a positive correlation with IR and TG/HDL-C ratio in CHD cases. The study conducted by Armato J. et al. [14] in 1,010 subjects at risk of diabetes showed that those with TG/HDL-C ratio in the highest quartile in men (≥ 3.0 mg/dL) and in women (≥ 2.0 mg/dL) had significantly higher blood pressure, poorer lipid profile, were more resistant to insulin as assessed by HOMA-IR, and had higher hs-CRP values.

Elevated TG and decreased HDL-C levels are known to be associated with the development of diabetes. Increased levels of TG induce cell apoptosis by increasing the levels of ceramide and nitric oxide (NO). On the other hand, HDL-C stimulates insulin secretion by interacting with ABCA1 (ATP G1 binding transporter) and inhibiting cell apoptosis [15]. An increase in the TG/HDL-C ratio was associated with impaired glucose homeostasis and insulin sensitivity better than classical lipid biomarkers. In this context, the TG/HDL-C ratio may be a useful parameter for relating four separate conditions such as inflammation, dyslipidemia, hyperglycemia, and atherosclerosis [16].

The results of this study showed that there was no statistically significant relationship between the TyG index and hs-CRP levels ($p = 0.58$) as a marker of chronic inflammation in people with prediabetes. This result is different from the research conducted by Kim G.R. et al. [9] who found that individuals with elevated hs-CRP levels had a significantly higher likelihood of developing IR, and this study confirmed that systemic inflammation reflected by high hs-CRP levels had an independent effect on IR as calculated by the TyG index. This study also reports that the TyG index value is superior in predicting IR than HOMA-IR. The TyG index describes two directions of IR, namely FPG primarily reflects hepatic IR whereas fasting TG primarily reflects adipocyte IR [8].

In acute conditions, hs-CRP levels rise sharply to more than 10 mg/L. High sensitive-CRP >1 mg/L is known to be associated with a mild risk of cardiovascular disease, levels of 1–3 mg/L are moderate risk, whereas >3 mg/dL represents a high risk of cardiovascular events. Low-grade inflammation is associated with prediabetes [17].

The difference between the results of this study and the results of other studies may be due to different prediabetes criteria. In this study we adopted IFG criteria where the PFG value was ≥ 100 mg/dL and < 126 mg/dL, while the study by Kim G.R. et al. used 2 criteria, IFG and IGT. Although IFG and IGT are both characterized by β cell dysfunction, the insulin secretory defect in IFG differs from that of IGT. Impaired glucose tolerance subjects have impaired late-phase insulin secretion and increased IR in skeletal muscle. In contrast, IFG subjects have impaired early-phase insulin secretion and increased IR in the liver. People with isolated IFG are more resistant to insulin, and those with isolated IGT show more severe insulin secretion deficits [18]. Insulin resistance in skeletal muscle is the main abnormality in diabetes, while IR in the liver is the beginning of hyperglycemia, which in turn causes a decrease in β cell function resulting in an increase in FPG levels [19]. Decreased hepatic insulin sensitivity, which is reflected by the HOMA-IR insulin sensitivity index, is detected early in patients with isolated IFG, while subjects with isolated IGT do not have hepatic insulin resistance, which may cause their FPG levels to be normal [20].

This study has several limitations. First, we did not perform an oral glucose tolerance test to include the IGT group as prediabetes. Second, factors that could affect IR activity and hs-CRP levels such as age, alcohol,

smoking, diet, and drugs were also not taken into account in this study.

Conclusions

There is no statistically significant relationship between TG/HDL-C ratio or TyG index and hs-CRP as a marker of chronic inflammation in people with prediabetes defined by IFG.

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Conflict of interest

None declared.

REFERENCES

1. Echouffo-Tcheugui JB, Selvin E. Prediabetes and What It Means: The Epidemiological Evidence. Annu Rev Public Health. 2021; 42: 59–77, doi: 10.1146/annurev-publhealth-090419-102644, indexed in Pubmed: 33355476.
2. Testa R, Bonfigli AR, Marra M, et al. In the light of the metabolic memory theory, should not all aged people with dysglycemia be treated? Rejuvenation Res. 2010; 13(5): 599–605, doi: 10.1089/rej.2010.1024, indexed in Pubmed: 20818982.
3. Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. Am J Clin Nutr. 2010; 91(1): 258S–261S, doi: 10.3945/ajcn.2009.28449C, indexed in Pubmed: 19906806.
4. Adukauskienė D, Čiginskienė A, Adukauskaitė A, et al. Clinical relevance of high sensitivity C-reactive protein in cardiology. Medicina (Kaunas). 2016; 52(1): 1–10, doi: 10.1016/j.medici.2015.12.001, indexed in Pubmed: 26987494.
5. Babic N, Valjevac A, Zaciragic A, et al. The Triglyceride/HDL Ratio and Triglyceride Glucose Index as Predictors of Glycemic Control in Patients with Diabetes Mellitus Type 2. Med Arch. 2019; 73(3): 163–168, doi: 10.5455/medarh.2019.73.163-168, indexed in Pubmed: 31404127.
6. Quispe R, Manalac RJ, Faridi KF, et al. Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: The Very Large Database of Lipids-4 (VLDL-4) study. Atherosclerosis. 2015; 242(1): 243–250, doi: 10.1016/j.atherosclerosis.2015.06.057, indexed in Pubmed: 26232164.
7. Yeh WC, Tsao YC, Li WC, et al. Elevated triglyceride-to-HDL cholesterol ratio is an indicator for insulin resistance in middle-aged and elderly Taiwanese population: a cross-sectional study. Lipids Health Dis. 2019; 18(1): 176, doi: 10.1186/s12944-019-1123-3, indexed in Pubmed: 31604438.
8. Low S, Khoo KC, Irwan B, et al. The role of triglyceride glucose index in development of Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2018; 143: 43–49, doi: 10.1016/j.diabres.2018.06.006, indexed in Pubmed: 29936253.
9. Kim GRi, Choi DW, Nam CMo, et al. Synergistic association of high-sensitivity C-reactive protein and body mass index with insulin resistance in non-diabetic adults. Sci Rep. 2020; 10(1): 18417, doi: 10.1038/s41598-020-75390-1, indexed in Pubmed: 33116232.
10. Bhowmik B, Siddiquee T, Mujumder A, et al. Serum Lipid Profile and Its Association with Diabetes and Prediabetes in a Rural Bangladeshi Population. Int J Environ Res Public Health. 2018; 15(9), doi: 10.3390/ijerph15091944, indexed in Pubmed: 30200612.
11. Kansal S, Kamble TK. Lipid Profile in Prediabetes. J Assoc Physicians India. 2016; 64(3): 18–21, indexed in Pubmed: 27731552.
12. Chakarova N, Tankova T, Atanassova I, et al. Serum lipid and hsCRP levels in prediabetes--impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Diabetes Res Clin Pract. 2009; 86(1): 56–60, doi: 10.1016/j.diabres.2009.04.005, indexed in Pubmed: 19674805.
13. Ramanujapura D, Umalakshmi V, Althaf MD. Study on Insulin Resistance and the Relationship of TG/HDL Cholesterol Index and HSCRP with Coronary Heart Disease. IJHCR. 2021; 4(8): 43–49.
14. Armato J, Reaven G, Ruby R. Triglyceride/high-density lipoprotein cholesterol concentration ratio identifies accentuated cardiometabolic risk. Endocr Pract. 2015; 21(5): 495–500, doi: 10.4158/EP14479.OR, indexed in Pubmed: 25667373.
15. Shimodaira M, Niwa T, Nakajima K, et al. Impact of serum triglyceride and high density lipoprotein cholesterol levels on early-phase insulin secretion in normoglycemic and prediabetic subjects. Diabetes Metab J. 2014; 38(4): 294–301, doi: 10.4093/dmj.2014.38.4.294, indexed in Pubmed: 25215276.
16. Scicali R, Giral P, D'Erasmo L, et al. High TG to HDL ratio plays a significant role on atherosclerosis extension in prediabetes and newly diagnosed type 2 diabetes subjects. Diabetes Metab Res Rev. 2021; 37(2): e3367, doi: 10.1002/dmrr.3367, indexed in Pubmed: 32558162.
17. Ghule A, Kamble TK, Talwar D, et al. Association of Serum High Sensitivity C-Reactive Protein With Pre-diabetes in Rural Population: A Two-Year Cross-Sectional Study. Cureus. 2021; 13(10): e19088, doi: 10.7759/cureus.19088, indexed in Pubmed: 34868746.
18. Colak A, Diniz G. Impaired glucose tolerance, obesity and inflammatory mediators. In: Chackrewarthy S, Diniz G. ed. Glucose Tolerance. IntechOpen, London 2012: 27–36.
19. Yip WCY, Sequeira IR, Plank LD, et al. Prevalence of Pre-Diabetes across Ethnicities: A Review of Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) for Classification of Dysglycaemia. Nutrients. 2017; 9(11), doi: 10.3390/nu9111273, indexed in Pubmed: 29165385.
20. Faerch K, Borch-Johnsen K, Holst JJ, et al. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? Diabetologia. 2009; 52(9): 1714–1723, doi: 10.1007/s00125-009-1443-3, indexed in Pubmed: 19590846.