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ARTIKEL PENELITIAN

Total-to-HDL Cholesterol Ratio and Visceral Adiposity Index Correlation in Type Two Diabetics with or without Ischemic Stroke

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Abstrak

Tujuan: Penelitian ini bertujuan untuk menganalisis perbedaan data klinis dan laboratorium, serta korelasi *Visceral Adiposity Index* (VAI) dengan parameter lain yang diamati pada penderita diabetes tipe 2 dengan atau tanpa stroke iskemik. **Metode:** Penelitian ini merupakan penelitian observasional analitik dengan desain potong lintang. Data klinis dikumpulkan langsung dari pasien, diikuti dengan pengumpulan data laboratorium. Analisis statistik dilakukan dengan uji perbandingan (Mann-Whitney atau independent T-tests) dan analisis korelasi (Pearson atau Spearman). **Hasil:** Pada kelompok stroke iskemik, rasio kolesterol total terhadap HDL dan VAI lebih tinggi secara signifikan (masing-masing p=0,033 dan 0,002) dibandingkan kelompok stroke non-iskemik. Rasio kolesterol total terhadap HDL dan VAI memiliki korelasi yang signifikan (p<0,001). Data klinis (lingkar pinggang dan VAI) serta laboratorium (kolesterol total, trigliserida, LDL-C, dan rasio kolesterol total terhadap HDL) berbeda secara signifikan pada pasien diabetes tipe 2 dengan atau tanpa stroke iskemik. **Kesimpulan:** Pada kedua kelompok diabetes, dengan atau tanpa stroke iskemik, terdapat korelasi yang bermakna antara VAI dengan rasio kolesterol total terhadap HDL.

Kata kunci: Dislipidemia; Stroke iskemik; Sindroma metabolik; Diabetes mellitus tipe 2; Obesitas visceral

Abstract

Objective*: The study aims to analyze clinical and laboratory data differences, also the correlation of Visceral Adiposity Index (VAI) with other observed parameters in type 2 diabetics with or without ischemic stroke.* ***Methods:*** *This study was conducted as analytic observational study with cross-sectional design. Clinical data were directly collected from patients, followed by laboratory data collection. There was a comparison (Mann-Whitney or independent T-tests) and correlation analysis (Pearson or Spearman).* ***Results:*** *In the ischemic stroke group, the total-to-HDL cholesterol ratio and VAI were significantly higher (p=0.033 and 0.002, respectively) than the non-ischemic stroke group. The total-to-HDL cholesterol ratio and VAI had a significant correlation (p<0.001). Clinical (WC and VAI) and laboratory data (total cholesterol, triglyceride, LDL-C, and total-to-HDL cholesterol ratio) differ significantly in type 2 diabetics with or without ischemic stroke.* ***Conclusion:*** *In both diabetes groups, with or without ischemic stroke, there was a significant correlation between VAI and the total-to-HDL cholesterol ratio.*

Keywords: *Dyslipidemia; Ischemic stroke; Metabolic syndrome; Type 2 diabetes mellitus; Visceral obesity*

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INTRODUCTION

Diabetes mellitus is the leading cause of cardiovascular disease and the eleventh leading cause of disability globally. According to the World Health Organization, the number of diabetics rose from 108 million in 1980 to 476 million in 2017.[1] The prevalence of diabetes mellitus patients in Indonesia was approximately 10.7 million (prevalence rate: 6.2 percent), placing Indonesia seventh in the world and fourth in the Asia continent.[2,3]

The development of diabetes may result in several complications. In general, it is classified as either macrovascular or microvascular complications.[4] Coronary heart disease, peripheral artery disease, and stroke are examples of macrovascular complications. Meanwhile, diabetic nephropathy, neuropathy, and retinopathy are examples of microvascular complications.[5] Diabetes mellitus patients are at a greater risk of ischemic stroke than non-diabetic patients due to greater atherosclerotic plaque size and volume of atheroma, as well as a smaller diameter of the arterial lumen.[6]

Fundamentally, atherosclerosis is a multifactorial phenomenon. Age, gender, smoking, obesity, and other factors have been shown to impact the process. However, metabolic syndrome (including dyslipidemia and diabetes mellitus) has been strongly linked with atherosclerosis development.[7–9]

Dyslipidemia in type 2 diabetes mellitus sufferers is associated with an increase in total cholesterol levels and a reduction in High-Density Lipoprotein (HDL) value.[10] Up to this point, the risk of vascular disease caused by dyslipidemia has been determined solely by changes in each of the lipid elements' parameters. However, the value of the total cholesterol to HDL ratio was found to be more determinative than changes in each lipid component parameter.[11,12] The total-to-HDL cholesterol ratio has been implicated in the development of ischemic stroke.[13]

As mentioned earlier, metabolic syndrome, which can be measured using the Visceral Adiposity Index (VAI) is another factor related to the risk of atherosclerosis in diabetes mellitus patients. A high Visceral Adiposity Index (VAI) has been considered as a risk factor for stroke in both men and women.[14] However, the findings of other studies indicate that the Visceral Adiposity Index (VAI) value is not related to the risk of cardiovascular disorder.[15]

Based on the aforementioned studies, it is reasonable to conclude that there are disagreements about the relationship between the total-to-HDL cholesterol ratio and the VAI in patients with type 2 diabetes mellitus. Furthermore, the lack of research on this correlation in Indonesia encourages researchers to investigate the comparison between clinical and laboratory data of the type 2 DM patients with or without ischemic stroke, in addition to the correlation between VAI and other observed data.

METHODS

This analytical observational research with a cross-sectional design was carried out in December 2018. This study's participants were outpatients with type 2 diabetes mellitus who were visiting Dr. Mohammad Hoesin hospital, a tertiary level hospital in Palembang, Indonesia. Direct interviews and waist circumference measurements were taken from patients who agreed to participate in the study and signed an informed consent form but had

not been diagnosed with hemorrhagic stroke. This study has been approved by the Institutional Ethics Committee of Sriwijaya University Faculty of Medicine (number: 256/kepfkrsmhfkunsri/2018).

A univariate analysis was used to identify the distribution of data on age, gender, clinical (waist circumference; WC, body mass index; BMI, and visceral adiposity index; VAI) and laboratory data (total cholesterol, triglyceride, High-Density Lipoprotein-Cholesterol; HDL-C, Low-Density Lipoprotein-Cholesterol; LDL-C, and total-to-HDL cholesterol ratio). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). VAI score was calculated as described by Amato, et.al.[16] using the following sex-specific formula:

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88xBMI)}\right) x \left(\frac{TG}{1.03}\right) x \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89xBMI)}\right) x \left(\frac{TG}{0.81}\right) x \left(\frac{1.52}{HDL}\right)$$

Bivariate analysis was done to determine the difference and correlation between observed variables. For the analysis of characteristics comparison between the ischemic and non-ischemic group, the Mann-Whitney U test or independent T-test was used according to the data distribution (normal: age, HDL-C, and LDL-C, otherwise was abnormal). The correlation analysis between each variable and VAI was conducted by using the Pearson (normal data distribution: age, HDL-C, LDL-C, and total-to-HDL cholesterol ratio) or Spearman test in the respective groups (with or without ischemic stroke). The level of significance was set at $p<0.05$. The IBM Statistical Package for Social Sciences (IBM® SPSS®) Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp.) was used for data processing and analysis.

RESULTS AND DISCUSSION

Sixty patients with type 2 diabetes mellitus were divided into two groups: those who had an ischemic stroke and those who did not, each with thirty participants.

Table 1. Distribution of Clinical and Laboratory Data[1]

Variables	Total, n=60 (M: 31, F: 29)	Ischemic Stroke, n=30 (M: 18, F: 12)	Non-Ischemic Stroke, n=30 (M: 13, F: 17)	p
Age (years)	56.00 (20.00-83.00) [a]	54.70 (13.58)[b]	55.73 (10.41)[b]	0.239[c]
Body Mass Index (kg/m^2)	24.21 (4.43)[b]	23.34 (3.48)[b]	24.20 (18.04-38.00) [a]	0.383[d]
Waist circumference (cm)	99.67 (19.59)[b]	111.83 (15.78)[b]	82.00 (66.00-124.00) [a]	<0.001[d*]
Visceral Adiposity Index	7.65 (1.24-127.25) [a]	8.00 (5.02-127.25) [a]	6.99 (4.00)[b]	0.002[d*]
Total cholesterol (mg/dL)	188.45 (49.94)[b]	211.00 (41.29)[b]	165.90 (97.00-290.00) [a]	<0.001[d*]
Triglyceride (mg/dL)	164.50 (40.00-392.00) [a]	183.50 (122.00-392.00) [a]	129.50 (40.00-366.00) [a]	<0.001[d*]
HDL-C (mg/dL)	37.85 (13.71)[b]	38.20 (12.36)[b]	37.50 (15.14)[b]	0.266[c]
LDL-C (mg/dL)	123.98 (45.88)[b]	142.40 (43.03)[b]	105.57 (41.59)[b]	0.001[c]
Total-to-HDL ratio	5.68 (2.17-23.14) [a]	5.63 (3.45-23.14) [a]	4.91 (1.62)[b]	0.033[d*]

[1] Note: Data was presented as (a) Median (minimum-maximum) or (b) Mean (SD); M: male; F: female.

Data analysis was conducted using (c) Independent T-test or (d) Mann-Whitney U Test
*data was considered as significant (p<0.05)

The distribution of type 2 diabetes mellitus patients was primarily in the age range of 50-59 years (45.00%), increased significantly when compared to the age range 40-49, and tended to decline until the oldest age range (80-89 years). The mean age distribution of patients was not significantly different (p>0.05), with a value of 55±13.58 years in patients with diabetes mellitus and ischemic stroke compared to 56±10.41 years in diabetic patients without ischemic stroke. Men predominated among patients with type 2 diabetes mellitus, accounting for 31 patients (51.67%), with 58.06 percent of whom had ischemic strokes. Meanwhile, 41.38 percent of the women in the study had ischemic strokes.

Table 2. Correlation between Visceral Adiposity Index and clinical parameters in the type 2 diabetes patient with or without ischemic Stroke[1]

Variable	Visceral Adiposity Index			
	Ischemic Stroke		Non-Ischemic Stroke	
	r	p	r	p
Age	-0.247	0.189	0.116	0.540[a]
Body Mass Index	-0.148	0.436	-0.144	0.449
Waist circumference (cm)	-0.127	0.502	-0.011	0.955
Total cholesterol (mg/dL)	-0.106	0.576	-0.363	0.049
Triglyceride (mg/dL)	0.599	<0.001	0.489	0.006
HDL-C (mg/dL)	-0.695	<0.001	-0.627	<0.001[a]
LDL-C (mg/dL)	-0.005	0.980	-0.223	0.237[a]
Total-to-HDL ratio	0.735	<0.001	0.656	<0.001[a]

[1] Note: [a]Correlation was measured using the Pearson correlation, otherwise was conducted using the Spearman test.

Most of the clinical data were found to be significantly different between both groups (p<0.05), except the body mass index. The same tendency was discovered when blood lipid variables were examined. Four of the five indicators tested revealed statistically significant differences (p<0.05) between the groups with or without ischemic stroke. HDL cholesterol levels were the only data that demonstrate insignificant findings. Table 1 displays the details.

Triglyceride (p<0.01), HDL cholesterol (p<0.001), and the total-to-HDL cholesterol ratio (p<0.001) exhibited significant correlations for those with or without ischemic stroke in the analysis of clinical and laboratory variables with the VAI. However, there is an additional measure that demonstrates a significant correlation in the non-ischemic stroke population, total cholesterol level (p<0.05). The strongest correlation, as quantified by the correlation coefficient, was found between the total-to-HDL cholesterol ratio and VAI in the ischemic stroke group (r=0.735) (Table 2).

Clinical and Demographical Characteristics

The majority of patients with type 2 diabetes mellitus in this study were

between the ages of 50-59 (45 %). This finding is consistent with the report of Basic Health Research (*Riset Kesehatan Dasar*, Riskesdas) in Indonesia by 2018, which states that the 55–64 years age group is dominant (6.3 percent of the total population).[17] However, data from the International Diabetes Federation (IDF) in 2019 revealed a different impression, with diabetes mellitus patients more likely to be found in older people, with two peaks in the 70-74 and 75-79 age groups (each about 20 percent of the total sufferers).[2] The mean age of patients with type 2 diabetes mellitus who had an ischemic stroke was about 55 years. This is consistent with the findings of Khoury et al., who discovered that the occurrence of ischemic stroke in patients with type 2 diabetes mellitus is highest at 65 years of age and decreases with older age.[18] Diabetes mellitus has also been identified as one of the major risk factors for the development of diabetes mellitus in patients aged less than 65 years (55 years in African Americans).[19]

Male patients slightly dominated type 2 diabetes mellitus patients in this study, accounting for 51.7 percent in total. The findings of this study are consistent with the International Diabetes Federation (IDF) report,[2] but differ from the Indonesian Basic Health Research report, which declares that the prevalence of diabetes in women (1.8%) is higher than in men (1.2%).[17]

Correlation Between Diabetes Mellitus, Ischemic Stroke, and VAI

According to the results of this study, male type 2 diabetes mellitus participants were more likely to experience ischemic stroke complications (58.06 percent) than female patients (41.38 percent). Studies from China and the DECODE cohort (Finland and Sweden) supported the findings of this study, which showed that male diabetes mellitus patients had a higher incidence of stroke than females.[20,21] In contrast, according to Zhao et. al., women with type 2 diabetes mellitus have more ischemic strokes than men.[22] Policardo et. al., on the other hand, stated that there was no difference in the risk of developing first ischemic stroke for both genders with diabetes (50 percent hazard ratio rise), but with advancing age, the risk reduction was lower in females.[23]

According to the clinical data, waist circumference and VAI in ischemic stroke patients were higher than in the non-ischemic stroke population. Previous research has found that these parameters are a reliable predictor for the development of cerebrovascular disease, particularly in men.[24]According to one study, the VAI and WC had higher sensitivities and specificities than BMI in predicting cardiovascular disease in adults.[25] Based on the equation model calculation, a significantly higher proportion of patients with central adiposity (increase in waist circumference) was discovered in the ischemic stroke population, and it is regarded as a more useful determinant than peripheral obesity (BMI).[26] Waist circumference was also found to be significantly higher in ischemic stroke patients than in non-ischemic stroke patients for both sexes.[27] Many events that can lead to an ischemic stroke, such as carotid plaque formation,[28] carotid artery stenosis,[28] brain infarction,[29] carotid intima thickening,[30] and overall atherosclerotic process,[16,31] have been noticed following an increase of VAI. Furthermore, VAI is a better predictor of a dysfunctional metabolic phenotype than traditional adiposity metrics (e.g., waist circumference, BMI, waist-to-height ratio, waist-to-hip ratio, and neck circumference).[32]

According to the theory, dyslipidemia has been recognized as a risk factor for ischemic stroke in type 2 diabetes patients, with a larger scale of disruption seen in this group compared to those without ischemic stroke.[10] We found significant differences in total cholesterol, triglycerides, LDL-C, and the total-to-HDL cholesterol ratio among diabetic patients with and without ischemic stroke. An Indian study confirmed our findings, revealing substantial differences in all lipid parameters between those patients with and without ischemic stroke ($p<0.001$).[33] However, the insignificant data on HDL level in our study could be attributed to a smaller number of participants in our study when opposed to prior studies (60 vs. 620). However, a Chinese study found that HDL-C levels in patients with and without ischemic stroke were not markedly different, in addition to total cholesterol.[34] Some cohort studies found a link between the total-to-HDL cholesterol ratio and the risk of having an ischemic stroke.[13,35] According to a subsequent study, the total-to-HDL cholesterol ratio was primarily associated with the occurrence of ischemic stroke in men (Hazard Ratio: 1.52, AUC: 0.868).[36]

Based on the current findings, there is a significant correlation between lipid parameters (triglyceride, HDL-C, and total-to-HDL cholesterol ratio) with VAI for both groups of diabetic patients. However, for the group without ischemic stroke, total cholesterol level was also significantly correlated with the VAI. This was consistent with the findings of Devi et al, who discovered a link between lipid profiles and cardiometabolic risk as measured by the VAI value.[37]Another study discovered a significant correlation between VAI and lipid profiles (especially triglycerides and HDL, similar to our study).[38]A separate study evaluated the Magnetic Resonance Imaging-based index for determining visceral adiposity had a significant influence on the total-to-HDL cholesterol ratio.[39]

Previous studies have linked dyslipidemia and metabolic syndrome to a higher risk of atherosclerosis. Its components, total-to-HDL cholesterol ratio, and VAI are equally useful in evaluating insulin resistance,[40] as well as adipocyte distribution and function.[41]In fact, the total-to-HDL cholesterol ratio is more enlightening than non-HDL cholesterol in estimating the cardiovascular risk of type 2 diabetes patients,[42] because it provides a more complete perspective of the balance of atherogenic and antiatherogenic cholesterol.[41]

There are several limitations to our study. First, no information on potential confounding factors such as treatment history or disease duration was obtained. Second, while the sample size was adequate, our population size was small in comparison to other comparable studies.

CONCLUSION

Type 2 diabetic sufferers with or without ischemic stroke demonstrate some significant differences in clinical data (WC and VAI) and lipid parameters (total cholesterol, triglyceride, LDL-C, and total-to-HDL cholesterol ratio). Correlation analysis revealed a significant relationship between VAI and lipid parameters (triglyceride, HDL-C, and total-to-HDL cholesterol ratio) in both groups, and with total cholesterol, exclusively in the non-ischemic stroke group.

It is suggested that future research will pay attention to other factors that may contribute to the incidence of ischemic stroke in type 2 diabetes mellitus patients, such as the history of cardiovascular disease, medication, duration of diabetes,

lifestyle, and so forth. The findings of this study are also intended to provide evidence for controlling the patient's blood lipid profile to reduce the risk of complications including ischemic stroke.

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CONFLICT OF INTEREST

None declared

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