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Hba1c levels correlated to lipoprotein-associated phospholipase A2 and monocyte HDL ratio in type 2 diabetes mellitus

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ABSTRACT

Background: In the last few decades, several hypotheses have been proposed to explain the pathogenesis of type 2 diabetes mellitus (T2DM) that links this disease with a systemic chronic inflammatory state. New predictors of lipoprotein-associated phospholipase A2 (Lp-PLA2) and monocyte HDL-c ratio (MHR) has been observed to predict atherosclerosis severity, progression of atherosclerosis and cardiovascular events. The study aims to evaluate correlation between HbA1c with Lp-PLA2 and MHR in patients with T2DM.
Methods: Analytic observational research with cross sectional design. HbA1c levels were measured by high-pressure liquid chromatography, Lp-PLA2 values using the ELISA method, and MHR values based on the ratio of absolute monocytes to HDL counted manually.
Results: The study was conducted on 42 DMT2 patients aged 34-74 years, mean value HbA1c, Lp-PLA2, and MHR were 8.16±2.10, 217.20±42.49, 10.55±6 11 respectively. Statistical analysis showed a positive correlation between HbA1c and Lp-PLA2 levels (p=0.046 and r=0.310), and there was a correlation between HbA1c levels and MHR values (p=0.038 and r=0.321).
Conclusion: A weak positive correlation between glycemic control (HbA1c) and atherosclerotic markers (Lp-PLA2 and MHR) in DMT2 patients.

INTRODUCTION

The prevalence of diabetes mellitus (DM) in Indonesia increased to 8.5% in 2018 with a 35-75 years of age, where the largest prevalence of T2DM is in the 55-64 year age range. Central Java occupies the 12th position in the population with the highest prevalence of DM in Indonesia.[1] Diabetes mellitus that is not adequately managed results in vascular complications divided into macrovascular complications such as coronary heart disease, peripheral vascular disease and stroke, and microvascular events such as retinopathy nephropathy and neuropathy.[2,3] DM complications can be prevented by optimal glycemic control.[4]

It is estimated that up to 25% of patients with newly diagnosed T2DM have evidence of chronic systemic inflammation when diagnosis exhibits various atherosclerotic plaque development stages.[5,6] Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been observed in recent years to be a predictor of heart disease. coronary and closely correlated with atherosclerosis.[7,8] There are several conflicting results regarding the Correlation between Lp-PLA2 and glycemic control in T2DM. Research by Castro et al.[9] found a negative correlation of Lp-PLA2 with HbA1c levels, analysis by Moise et al.[10] states that there is a negative correlation of Lp-PLA2 with plasma glucose, while in the study by JL Sanchez Quesada, et al.[11] and Xin et al.[12] found a positive correlation between HbA1c and Lp-PLA2 levels in T2DM patients.

The most recent marker of cardiovascular disease is the monocyte HDL-c ratio. These markers can be used to predict the severity of atherosclerosis, progression of atherosclerosis and cardiovascular events. Monocyte HDL-c Ratio has advantages over the value of monocytes or HDL alone because it has two indicators, namely the pro-inflammatory and anti-inflammatory pathways.[13,14,15] Research conducted on the T2DM population by Karatas et al.[15] and Onalan et al.[16] showed an increase in MHR and the severity of patients with T2DM2.

Endothelial dysfunction is almost always found in T2DM patients, because chronic hyperglycemia can disrupt Nitic Oxide (NO) production and activity, while endothelium has intrinsic limitations in self-repair. Endothelial dysfunction refers to conditions in which the endothelium loses its physiological function, such as the tendency to increase vasodilation, fibrinolysis, and anti-aggregation.[17,18]

Endothelial damage will lead to coronary atherosclerotic lesions, leading to cardiovascular disease (CVD).[2,4,19]

Evidence shows that diabetes complications can be prevented with optimal glycemic control, many studies have been conducted regarding prevention and management efforts, both for diabetes and its complications.[2,4,20] Laboratory tests commonly used for glycemic monitoring status include blood glucose levels (plasma or capillary) and glycic hemoglobin (HbA1c) where HbA1c is the "gold standard" assay in many centers.[2,4,20,21]

The recognition of the role of inflammation in atherogenesis has led to the search for molecules that promote the vascular inflammatory response.[22] Lipoprotein enzymes associated phospholipase A2, a secretory product of inflammatory cells that binds mainly to lipoproteins containing apolipoprotein B such as LDL.[23] Lipoprotein-associated phospholipaseA2 levels can be affected by several factors. Research by Chen et al.[24] proved that the activity levels of Lp-PLA2 were lower in Taiwanese women with a vegetarian diet. Research by Paik et al.[25] stated that age ≥ 75 years and body mass index (BMI)> 30kg / m2 indicates higher Lp-PLA2 levels. The increased Lp-PLA2 activity in obese and women aged 65-89 years is consistent with previous studies which reported a weak but significant correlation between age and Lp-PLA2 activity.[26,27] Research by Hatoum et al.[26] also stated that 15g of alcohol consumption per day was associated with low Lp-PLA2 levels, while Lp-PLA levels increased in smokers.[28]

An increase in the number of monocytes in the body is often associated with an inflammatory process that can play a role in the atherosclerosis process. Furthermore, HDL molecules can inhibit the activation and spread of monocytes, in addition to inhibiting the work of activated monocytes. This makes MHR possible to predict the severity of atherosclerosis, progression of atherosclerosis and cardiovascular events. Monocyte HDL Ratio has an advantage over monocytes or HDL value alone because it has 2 indicators, namely pro-inflammatory and anti-inflammatory pathways.[13,14] Monocytes play an essential role in the

Table 1. Data on the characteristics of research subjects

Subject characteristics	Mean ± SD	Median (min - max)
Age (years)	56.83 ± 11.11	57 (35 - 74)
BMI (kg/m²)	25.52 ± 3.04	25.95 (16.5 - 30)
HDL (mg/dL)	46.17 ± 12.73	43 (26 - 90)
LDL (mg/dL)	130.05 ± 36.42	129 (60 - 228)
SGOT (U/L)	22.17 ± 6.34	21 (8 - 32)
SGPT (U/L)	22.24 ± 7,11	21.5 (9 - 32)
Ureum (mg/dL)	34.57 ± 11.6	32.5 (17 - 50)
Creatinine (mg/dL)	1.04 ± 0.33	1.03 (0.52 - 1.3)
Hemoglobin (g/dL)	13.22 ± 0.88	13.2 (11.7 - 15.1)
Platelets (103/uL)	313.60 ± 80.02	298.5 (194 - 572)
Leukocytes (103/uL)	7.32 ± 1.61	7.25 (4 - 11)
Monocytes (103/uL)	0.42 ± 0.14	0.4 (0.1 - 0.7)
HbA1c (%)	8.14 ± 2.07	7.9 (5 - 14.1)
Lp-PLA2 levels (ng/ml)	217.20 ± 42.49	223.8 (80.2 - 288)
MHR	9.93 ± 4.23	9.25 (2.38 - 18.46)

Abbreviation: SB: standard deviation; min: minimum; max: maximum; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SGOT: Glutamic Oxaloacetic Transaminase Serum; SGPT: Glutamic Pyruvic Transaminase Serum; HbA1c: Hemoglobin A1c; MHR: Monocyte HDL Ratio; Lp-PLA2: Lipoprotein-associated phospholipase A. Normal values of Lp-PLA2 21.2 - 167 ng/ml

development of diabetes complications. Monocyte count has been shown to be associated with insulin resistance, type 2 diabetes, coronary artery disease, micro diabetes, and macrovascular complications.[29-32] Monocyte HDL Ratio consists of monocyte components and also HDL so that conditions that affect monocytes and HDL will also be able to affect MHR.[13,14] Study by Kolovou et al.[33] states that there are differences in lipid profiles in men and women, where men's HDL levels are lower than in women. The study by Chen et al.[34] in the T2DM population proved that MHR is influenced by therapy to lower cholesterol, especially the statin group and the male sex has a higher MHR value. Wu et al.[35] stated that old age more than 70 years, high pulse rate in men, abnormal leukocyte counts influence the MHR value. The study aims to evaluate correlation between HbA1c with Lp-PLA2 and MHR in patients with T2DM.

METHODS

This study was an analytic observational study with a cross sectional design. Sampling was done by consecutive sampling. This research was conducted at the Diponegoro National Hospital (RSND) Semarang. Lipid profile examinations

(HDL, LDL, triglyceride levels), liver function tests (SGOT, SGPT levels), kidney function tests (urea levels, creatinine) were carried out at the Semarang RSND laboratory, examination of HbA1c levels, routine hematology is performed in private laboratories. Levels of Lp-PLA2 were carried out in the GAKI laboratory of the Faculty of Medicine, Semarang-Indonesia. This study started in July 2019 until February 2020. Inclusion criteria in this study were female sex, adult age, normal body temperature (temperature 36.5 - 37.2oC), Hb levels 11.7 - 15.5 g/dL, the number of leukocytes 3.6 - 11.103 /μL, SGOT <31 mg/dL, SGPT <32 mg/dL, urea 10-50 mg / dL, creatinine 0.6 - 1.3 mg / dL, BMI 18.5 to ≤ 30kg / m², non-vegetarian. Smoking and alcohol consumption exclusion criteria.

DATA ANALYSIS

The data were processed using the IBM SPSS Statistic version 25 program. The normality test was performed using Saphiro-Wilk.After the transformation, data that were not normal were carried out by the Spearman correlation test for bivariate analysis between Lp-PLA2 with HbA1c and MHR with HbA1c. Significance was stated at $p < 0.05$.
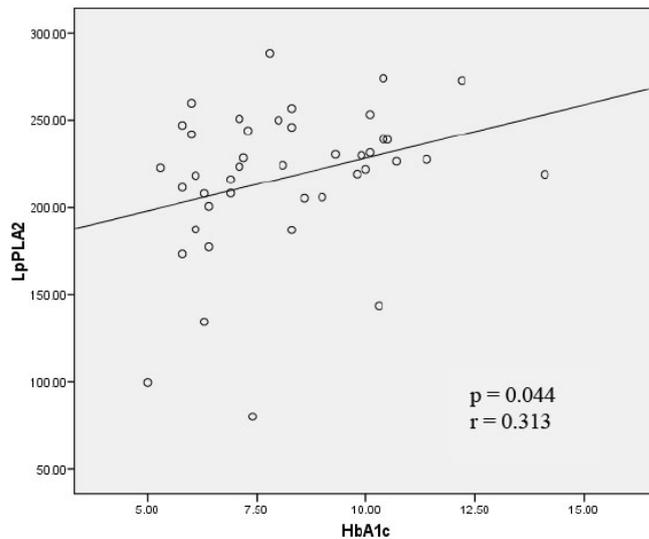
Figure 1. Scatter plot graph of the Correlation between HbA1c and Lp-PLA2 levels
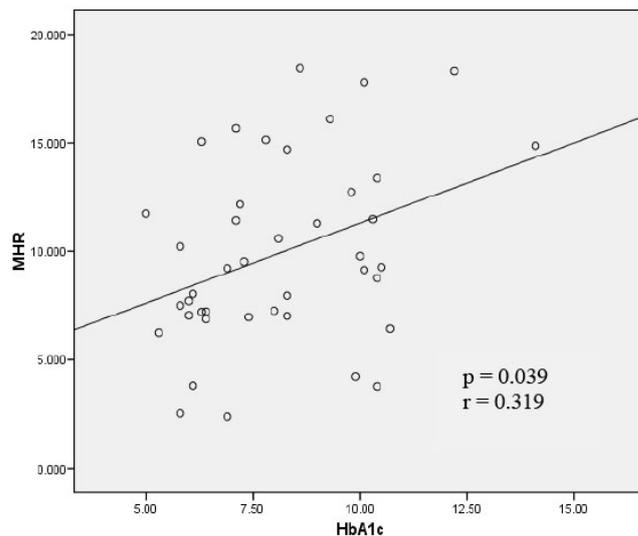

Figure 2. Scatter plot graph of the Correlation between HbA1c and MHR levels

RESULT

The screening results obtained 42 samples of T2DM patients who met the inclusion and exclusion criteria and were willing to sign an informed consent. Table 1 shows characteristics of study participant.

The results of the Correlation test between HbA1c and Lp-PLA2 levels showed p = 0.044 and r = 0.313, meaning that there was a weak positive correlation between the two variables. The scatterplot graph of the Correlation between HbA1c and Lp-PLA2 levels in T2DM patients can be seen in Figure 1.

The results of the correlation test between HbA1c and MHR levels showed p = 0.039 and r = 0.319, meaning that there was a weak positive correlation between the two variables. The scatterplot graph of the Correlation between HbA1c and MHR levels in T2DM patients can be seen in Figure 2.

DISCUSSION

This study indicates a significant correlation between the HbA1c value and the LpPLA2 level in T2DM patients. This study is in line with the research of Sanchez et al.[11] and Xin et al.[12] which found a positive correlation between HbA1c levels and Lp-PLA2 in T2DM patients. The increased risk of cardiovascular disorders in T2DM patients is partly due to lipoprotein modification and chronic inflammation.[11] T2DM patients have atherogenic dyslipidemia, characterized by hypertriglyceridemia, high LDL cholesterol levels, and hyper-apoB. LpPLA2 enzyme, a secretory product of inflammatory cells that binds mainly to lipoproteins containing apolipoprotein B such as LDL.[23] The results of this study indicate that poor glycemic control has a positive correlation with an increase in Lp-PLA2 levels that can be detected in the serum of T2DM patients. Elevated HbA1c levels indicate an increased risk of atherosclerosis and cardiovascular disorders in T2DM patients. In accordance with the study by Hatoum et al.[26] concluded that Lp-PLA2 activity was strongly associated with CVD incidence in T2DM, observing 740 men and 777 women with diabetes.[26]

Study by Castro et al.[9] showed a negative correlation between Lp-PLA2 and HbA1c (r = -0.319; p = 0.039) but in DMT1 subjects. In type 1 diabetes mellitus, the lack of hyperglycemia control only causes a slight increase in LDL cholesterol and triglycerides and a slight change in HDL cholesterol. Once hyperglycemia is corrected, lipoprotein levels generally return to normal. However, patients with T2DM are identified as "diabetic dyslipidemia," which is characteristic of insulin resistance syndrome, the symptoms are high triglyceride levels (100-300 mg/dL), low HDL levels (<30 mg/dL) and there are qualitative changes in LDL particles, i.e. produce small solid particles that are more susceptible to oxidation making them more atherogenic.[36]

Research by Sanchez et al.[11] showed a strong positive correlation between Lp-PLA2 and HbA1c (r = 0.494, p = 0.001) studies by Li et al.[12] also showed a strong positive correlation between Lp-PLA2 levels with HbA1c (r = 0.45, p<0.05).[12] Both of these studies were conducted in a population with a close age range, so that the factors that affect the results can be minimized. Study by Seals et al.[37] shows that people over 65 have experienced

vascular endothelial dysfunction that causes atherosclerosis.[37] In our study, there was a fairly large age range among the study population. This may be a factor in the weak positive association results.

The results of this study showed a significant correlation between HbA1c levels and MHR levels in the study subjects of T2DM patients. To the best of the authors' knowledge, no studies have linked HbA1c to MHR levels, but this study is in line with Onalan et al.[16] study which showed an association of diabetes with MHR (r = 0.241, p <0.001) in diabetes and healthy control group. Monocytes play an essential role in various stages of atherosclerosis from initiation to progression of complications. Monocytes are more often able to recognize sufficiently the monocyte chemoattractant protein-1 (MCP-1) so that they are more easily recruited in areas experiencing inflammation.[38] Monocytes play a role in the progression of atherosclerosis.[39] High-Density Lipoprotein levels through several mechanisms, namely the efflux of excess cholesterol at the cellular level, preventing LDL from being modified by preventing the occurrence of ox-LDL and maintaining endothelial function through anti-inflammatory and anti-thrombotic mechanisms.[40,41,42] An increase in the number of monocytes in the body is often associated with an inflammatory process that can play a role in the atherosclerosis process. Furthermore, HDL molecules can inhibit the activation and spread of monocytes, in addition to inhibiting the work of activated monocytes. This makes MHR possible to predict the severity of atherosclerosis, progression of atherosclerosis and cardiovascular events.[13,14]

The results of this study indicate that poor glycemic control has a positive correlation with increased MHR levels in T2DM patients. This study is in line with previous studies, which showed that MHR levels increased in line with the severity of the disease course in T2DM patients, which led to complications of T2DM, for example in renal failure and cardiovascular disorders.[15,16]

CONCLUSIONS

There is a weak positive Correlation between HbA1c levels and Lp-PLA2 levels in T2DM patients. There is a weak positive Correlation between HbA1c levels and MHR values in T2DM patients.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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ETHICAL STATEMENT (ETHICAL CLEARANCE)

Ethical Committee Faculty have approved this study of Medicine, Universitas Diponegoro with ethical clearance reference number No.19/EC/KEPK/FK-UNDIP/II/2020. All study protocol in accordance to Helsinki declaration of human rights.

AUTHOR CONTRIBUTION

All authors contributed toward drafting and revising the paper and agree to be accountable for all aspects of the work.

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