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Soluble CD163 and small dense LDL cholesterol levels in type 2 diabetes patients

CD163 soluble y niveles de colesterol LDL denso pequeño en pacientes con diabetes tipo 2

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SUMMARY

Introduction: *The sdLDL cholesterol proportion is a better marker for the prediction of cardiovascular diseases (CVDs). Macrophages play a crucial role in both initiation and progression of atherosclerosis, the underlying mechanism of CVDs. This study investigated the correlation between soluble CD163 as a biomarker macrophage activation and sdLDL cholesterol in type 2 diabetes mellitus (T2DM) subjects for the first time.*
Methods: *This study was an observational analytic cross-sectional study involved 40 patients with T2DM in Surabaya, Indonesia. The sdLDL was measured using a direct enzymatic colorimetric method using Architect c8000. The levels of sCD163 were measured by a quantitative enzyme immunoassay technique using a specific monoclonal antibody for human CD163 using Quantikine® Elisa produced by R&D Systems Inc., USA.*
Results: *The average level of HbA1c in this study was 8.01 ± 1.39 %, and more than half of the subjects had HbA1c levels >8 % that revealed most of the patients in this study were in poor glycemic control. The average sdLDL cholesterol level in this study was 40.80 ± 19.14 mg/dL, and the mean of soluble CD163 was 741.22 ±41.55 ng/mL. There were no differences in gender (male or female), glycemic control (<8 % vs >8 %), hypertension, and smoking on sCD163 levels and sdLDL cholesterol levels. We found a positive correlation between the soluble CD163 level with sdLDL (r=0.440, p=0.004).*
Conclusion: *The atherogenic lipoprotein fraction sdLDL cholesterol level correlated with soluble CD163 level. This could be a new link between lipid dysregulation, innate immunity, and atherosclerosis in T2DM.*

Keywords: *sdLDL, soluble CD163, atherosclerosis, T2DM.*

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RESUMEN

Introducción: *La proporción de sdLDL colesterol es un mejor marcador para la predicción de enfermedades cardiovasculares (ECV). Los macrófagos juegan un*

papel crucial tanto en el inicio como en la progresión de la aterosclerosis, el mecanismo subyacente de las ECV. Este estudio investigó la correlación entre CD163 soluble como un biomarcador de activación de macrófagos y colesterol sdLDL en sujetos con diabetes mellitus tipo 2 (T2DM) por primera vez.

Métodos: *Este estudio fue un estudio transversal analítico observacional que involucró a 40 pacientes con DM2 en Surabaya, Indonesia. La sdLDL se midió mediante un método colorimétrico enzimático directo usando Architect c8000. Los niveles de sCD163 se midieron mediante una técnica de inmunoensayo enzimático cuantitativo usando un anticuerpo monoclonal específico para CD163 humano usando Quantikine® Elisa producido por R&D Systems Inc., EE.UU.*

Resultados: *El nivel promedio de HbA1c en este estudio fue 8,01 ± 1,39 %, y más de la mitad de los sujetos tenían niveles de HbA1c> 8 % que revelaron que la mayoría de los pacientes en este estudio tenían un control glucémico deficiente. El nivel medio de colesterol sdLDL en este estudio fue 40,80 ± 19,14 mg/dL y la media de CD163 soluble fue 741,22 ± 41,55 ng/mL. No hubo diferencias en sexo (hombre o mujer), control glucémico (<8 % vs >8 %), hipertensión y tabaquismo en los niveles de sCD163 y los niveles de sdLDL colesterol. Se encontró una correlación positiva entre el nivel de CD163 soluble con sdLDL (r= 0,440, p= 0,004).*

Conclusión: *El nivel de sdLDL colesterol de la fracción de lipoproteínas aterogénicas se correlacionó con el nivel de CD163 soluble. Este podría ser un nuevo vínculo entre la desregulación de lípidos, la inmunidad innata y la aterosclerosis en la DM2.*

Palabras clave: *sdLDL, CD163 soluble, aterosclerosis, DM2.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is related to an increase in the risk of coronary heart disease incidence, ischemic stroke, and mortality. T2DM also affects life quality by increasing the risk of heart failure, peripheral artery insufficiency, and microvascular complications. It is also affected life expectancy by decreasing about 4–8 years in patients with diabetes, compared to individuals without diabetes (1). The mechanisms of the pathogenesis of cardiovascular diseases (CVDs) in T2DM are associated with epigenetic, genetic, and cell-signaling defects in inter-related metabolic and inflammatory pathways (2). The association of T2DM and CVDs is affected by environmental factors and phenotypes of the patients. Patients with T2DM are often accompanied by other conditions such as dyslipidemia, hypertension, inflammation, procoagulant state, or thrombosis, representing risk factors for CVDs (3).

T2DM involves abnormalities in carbohydrate and lipid metabolism. Dyslipidemia is one of the comorbidities often present in patients with T2DM, which may stimulate and facilitate atherogenesis and the atherosclerosis process. Proteins help the distribution of lipids as their properties allow them to remain in the circulatory system. Those proteins are categorized according to their molecular density into very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Along with triglycerides, lipid clusters lipoproteins circulate along vessels to distal organs and tissues (3,4). LDL cholesterol plays a crucial role in the development and progression of atherosclerosis and CVD, especially in T2DM (5).

LDL consists of several subclasses with different sizes and densities of particles, including large buoyant LDL (lbLDL), intermediate LDL, and small dense LDL (sdLDL) (6). It has been well established that sdLDL has a greater atherogenic potential than other LDL sub-fractions. The proportion of sdLDL is a better predictor of cardiovascular disease than total LDL-C. The circulation time of sdLDL is longer than that of large LDL particles that are cleared from the bloodstream through the interaction with the LDL receptor. Circulating sdLDL has a lower affinity to LDL receptors, and multiple atherogenic modifications in blood plasma, such as desialylation, glycation, and oxidation, increase its atherogenicity (5,7,8). Circulating sdLDL cholesterol levels are also associated with systemic inflammation (9). Dyslipidemia and systemic inflammation, which is the leading hypothesis to explain the pathogenesis of atherosclerosis, are related to sdLDL cholesterol (10,11).

Immune system activation is associated with T2DM progression. Hyperglycemia induces an apoptotic mechanism producing inflammation in pancreatic beta cells. IL-6 stimulates apoptosis in pancreatic islets together with other inflammatory

cytokines and acts as a predictor for the progression of T2DM. Oxidative stress may also potentiate the generation of free radical oxygen and proinflammatory cytokines that disrupts and destroys the beta cells. Adaptive and innate immunity responses are involved in adipose tissue inflammation in T2DM. The phenotype switching of macrophages from predominantly anti-inflammatory M2-type to increased proportions of proinflammatory M1-type macrophages plays a critical role in the stimulation and progression of islet inflammation. The recruitment of B cells and T cells precedes adipose tissue infiltration by macrophages (12-14).

CD163 is a receptor for haptoglobin-hemoglobin complexes and is expressed solely on macrophages and monocytes. The extracellular portion of CD163 circulates in the blood as a soluble protein (sCD163) and increases acutely due to metalloproteinase-mediated cleavage near the cell membrane during inflammation and macrophage activation. The sCD163 is very useful as a biomarker of macrophage activation in various inflammatory diseases. Macrophage infiltration of adipose tissue and the liver is strongly related to the progression of T2DM (15,16). The sCD163 was associated with myocardial infarction and coronary artery disease in the population cohort (17), carotid intima-media thickness in older people (18). The sCD163 also accelerates atherosclerosis in systemic lupus erythematosus (19) and increases vulnerable plaque in human immunodeficiency virus (HIV) patients (20).

Therefore, we conduct this study to find the relationship between the sCD163 as a marker of macrophage activation and sdLDL as a predictor of CVDs risk in patients with T2DM from a tertiary referral hospital in Surabaya, Indonesia.

MATERIAL AND METHOD

Design and Population Study

This study was a cross-sectional analytic observational study that involved 40 participants with T2DM from the diabetes outpatient clinic in Dr. Soetomo general hospital, Surabaya, Indonesia. Subjects with T2DM with age more than 40 years old were recruited in the study. All subjects were on statin therapy as a part of diabetes management. Diagnosis of T2DM based on medical record or fulfilled Indonesian Society of Endocrinology Criteria 2015 (21). Subjects with acute complications of diabetes (such as ketoacidosis, sepsis, and acute infection), renal and liver impairment, chronic hepatitis, liver cirrhosis, pregnancy, HIV infection, steroid therapy, and autoimmune disease were excluded from the study. All participants gave their informed consent to participate in the study approved by the local Ethics Committee.

Data Collection

Interview and vital signs were performed in all subjects. A digital sphygmomanometer measured blood pressure (BP) after allowing the patients to rest for 15 minutes before the examination. Hypertension was defined by JNC VIII criteria (22), which subjects with systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Weight and height were measured in all subjects, and body mass index (BMI) was calculated. The smoking status was assessed by recording the habit and duration of smoking, which active smoker was defined as the subject had >100 cigarettes during life. Blood samples were collected after an overnight fast to measure sCD163 and sdLDL cholesterol levels, biochemical variables such as triglycerides, total cholesterol, HDL, LDL cholesterol. Fasting plasma glucose, 2 hours postprandial glucose, and HbA1c levels were also measured using standard techniques. The sdLDL was measured using a direct enzymatic colorimetric method using Architect c8000. The levels of sCD163 were measured by a quantitative enzyme immunoassay technique using a specific monoclonal antibody for human CD163 using Quantikine® Elisa produced by R&D Systems Inc., USA.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation. Categorical variables were expressed as group

percentages. The mean of the group was analyzed using Student t-test analysis. The distribution of data was analyzed using the Kolmogorov-Smirnov test. Pearson's correlation was utilized to demonstrate the correlations between sCD163 and sdLDL levels if the data distribution was normal.

RESULTS

Clinical characteristic of the subjects

General characteristics of subjects such as age, sex, height, weight, BMI, and clinical features of T2DM, hypertension, and lipid profile were described in Table 1. There were 17 male and 23 female subjects. The average BMI was 25.66 ± 2.91, and the duration of diabetes was 8.13 ± 5.77 years. The average level of fasting plasma glucose was 150.20 ± 61.97 mg/dL, postprandial plasma glucose was 214.20 ± 33.64 mg/dL, and HbA1c was 8.13 ± 5.77 mg/dL. There were no different characteristics between male and female subjects in this study.

Table 1

Clinical characteristics of subjects

Characteristics	Mean ± SD		
	All (n=40)	Male (n=17)	Female (n=23)
Age (years old)	59.55 ± 8.14	60.82 ± 7.85	59.55 ± 8.14
Height (cm)	156.93 ± 7.35	162.88 ± 5.85	156.93 ± 7.35
Weight (kg)	63.20 ± 8.06	63.91 ± 8.39	63.20 ± 8.06
Body Mass Index (BMI)(kg/m^2)	25.66 ± 2.91	24.04 ± 2.37	26.86 ± 2.72
Type 2 Diabetes Mellitus			
- Duration (years)	8.13 ± 5.77	8.52 ± 5.99	7.83 ± 5.73
- Fasting plasma glucose (mg/dL)	150.20 ± 61.97	151.82± 67.44	149.00 ± 59.13
- Postprandial plasma glucose (mg/dL)	214.20 ± 33.64	227.29 ± 83.44	204.52 ± 67.39
- HbA1c (%)	8.01 ± 1.39	8.00 ± 1.50	8.02 ± 1.33
Hypertension			
- Systolic blood pressure (mmHg)	144.20 ± 20.15	145.58 ± 6.00	143.17 ± 3.43
- Diastolic blood pressure (mmHg)	87.57 ± 10.72	86.30 ± 1.88	89.29 ± 3.09
Lipid Profile			
- Total cholesterol (mg/dL)	213.20 ± 33.64	214.23 ± 24.58	212.43 ± 39.56
- LDL cholesterol (mg/dL)	145.02 ± 33.92	148.41 ± 30.21	142.52 ± 36.89
- HDL cholesterol (mg/dL)	45.25 ± 11.98	42.47 ± 7.20	47.30 ± 14.36
- Triglyceride (mg/dL)	172.07 ± 51.38	170.47 ± 44.43	173.26 ± 56.93

Soluble CD163 levels

The average levels of sCD163 in this study were 741.22 ± 41.55 ng/mL. There were no differences of gender (male or female), glycemic control (< 8 % versus > 8 %), hypertension, and smoking on sCD163 levels were found in this study (Table 2).

Small dense LDL cholesterol levels

The average levels of sdLDL cholesterol in this study were 40.80 ± 19.14 mg/dL. The sCD163 levels in this study were not affected by gender (male or female), glycemic control (<8 % versus >8 %), hypertension, and smoking (Table 3).

Table 2

Soluble CD163 level in all subjects

Variable	n (%)	Mean ± SD (ng/mL)	p
All subjects	40 (100)	741.22 ± 41.55	
Gender			
- Male	17 (42.50)	729.97 ± 64.51	0.559
- Female	23 (57.50)	749.53 ± 55.25	
Glycemic control			
- <8 %	19 (47.50)	732.64 ± 259.22	0.784
- >8 %	21 (52.50)	748.97 ± 271.03	
Hypertension			
- Yes	30 (75.00)	728.48 ± 260.56	0.522
- No	10 (25.00)	779.42 ± 277.47	
Smoking			
- Yes	7 (12.50)	634.92 ± 261.03	0.817
- No	33 (87.50)	763.76 ± 260.80	

Table 3

Small dense LDL level in all subjects

Variable	n (%)	Mean ± SD (mg/dL)	p
All subjects		40 (100)	40.80 ± 19.14
Sex			
- Male	17 (42.50)	40.87 ± 14.59	0.132
- Female	23 (57.50)	40.75 ± 22.24	
Glycemic control			
- <8 %	19 (47.50)	42.63 ± 20.74	0.412
- >8 %	21 (52.50)	39.14 ± 17.92	
Hypertension			
- Yes	30 (75.00)	39.23 ± 17.97	0.437
- No	10 (25.00)	45.52 ± 22.67	
Smoking			
- Yes	7 (12.50)	48.88 ± 22.57	0.592
- No	33 (87.50)	39.08 ± 18.27	

Correlation between soluble CD163 and sdLDL

The distribution of data was analyzed using the Kolmogorov-Smirnov test. The data distribution in this study was normal, then the correlation between sCD163 and sd LDL cholesterol levels was continued to analyze using the Pearson correlation test. There was a significant correlation between sCD163 and sd LDL cholesterol levels with p 0.004 and a correlation coefficient of 0.440 (Figure 1).

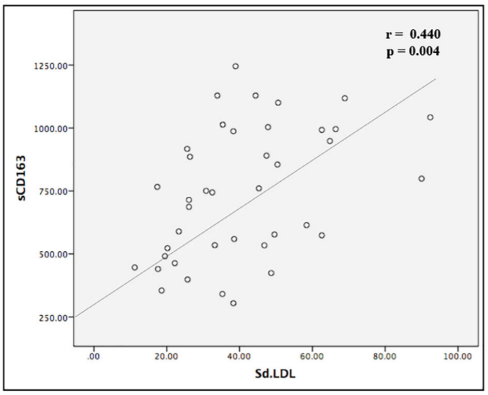

Figure 1. The correlation plot between sCD163 and sdLDL in all subjects.

DISCUSSION

We found there was a positive correlation between soluble CD163 and sdLDL in T2DM patients. The CD163 is a member of the scavenger receptor superfamily, categorized into class B, and its soluble form is a marker of activated M2 macrophages. Increased plasma levels of sdLDL were one of the predictors of atherosclerosis and cardiovascular disease in many previous studies. A positive correlation between soluble CD163 and sdLDL showed there is a link between innate immunity and the atherogenic process in the T2DM population.

Our study was also the first study that measured the soluble CD163 in the diabetes population in Indonesia. The mean of soluble CD163 levels was 741.22 ng/mL (similar to 0.741 mg/L). Although we did not have soluble CD163 data in a healthy population in Indonesia, another study in Scandinavia found that soluble CD163 levels were 0.7–3.9 mg/L in healthy individuals (16). Gender, glycemic control, hypertension, and smoking did not affect soluble CD163 levels in this study. The average level of HbA1c was 8.01 ± 1.39 %, above the target of HbA1c for T2DM. More than half of the subjects had HbA1c levels > 8 % that revealed most subjects in this study were in poor glycemic control. It was similar to the Diabcare Asia study that showed the mean levels of HbA1c in Indonesia was 8.3 ± 2.2 %, and 48.5 % of patients had HbA1c levels > 8 % (23).

Another study in subjects with type 1 diabetes mellitus, that gender did not associate with soluble CD163 levels (24), but it is different from a study in Arab Saudi, which is showed that systolic and diastolic blood pressure had an association with soluble CD163 (25). Smoking also did not give a different effect to soluble CD163 in the HIV population (26), similar to this study.

In this study, we assessed the relationship between soluble CD163 as a marker of macrophage inflammation with sdLDL as a predictor of CVD risk in the T2DM population in a tertiary referral hospital in Indonesia. This study used sdLDL cholesterol level instead of LDL cholesterol, because many individuals with LDL levels within the normal range, still develop atherosclerosis and cardiovascular disease. This implies a significant heterogeneity of LDL-particles, as the sub-fraction of small dense LDL exhibits enhanced atherogenic potential. Small dense LDL has a stronger predisposition for oxidation, lower LDL-receptor affinity, and an increased accumulation within the vascular wall (27,28). Several studies have established an association of elevated sdLDL levels with atherosclerosis and cardiovascular disease (5,7-9). The other study showed that high levels of plasma sdLDL were associated with an increased risk of major cardiovascular events among T2DM patients with coronary artery disease (29).

Monocytes and macrophages have been involved in all stages of atherogenesis, from initiation and progression to destabilization and rupture of atherosclerotic lesions. This was shown in stable coronary artery disease patients was shown there was the association of sdLDL serum levels and circulating monocyte subsets. Circulating monocytes used three distinct subtypes according to their surface expression of CD14 and CD16 (28).

During the early stages of atherosclerosis, oxidized low-density lipoproteins accumulated in the intima, stimulate the activation of endothelial cells and vascular smooth muscle cells, inducing expression and secretion of proinflammatory cytokines, and adhesion molecules that attract monocytes within the arterial wall. Monocytes continued to differentiate into the macrophages to remove oxidized LDL. There are two phenotypes of macrophages, the M1-type macrophage has a direct effect on pathogen killing, while the M2-type macrophage expresses high levels of scavenging molecules and anti-inflammatory cytokines (30). M2-type macrophages express high levels of CD163, a member of the scavenger receptor cysteine-rich family (30). The soluble form of CD163 is a normal constituent in plasma and is generated by proteolytic cleavage of CD163 at the cell surface. This receptor is now known as an immunomodulatory of atherosclerotic plaque, with anti-inflammatory and anti-atherogenic function. The soluble CD163 levels are increased in patients with atherosclerosis (28).

There were several limitations of this study that have to be considered. First, this is a single-center study from a tertiary referral hospital with a small number of patients. Second, the cross-sectional

study design only allows us to find associations between soluble CD163 and sdLDL, but could not define the causal relationship. Third, we did not differentiate subjects with CVD and non-CVD in this study. However, this study indicates a link between innate immunity and lipid metabolism in atherosclerosis-related diseases, such as T2DM.

CONCLUSION

This study gives evidence for the first time for a positive correlation between soluble CD163 as a marker of macrophage activation and atherogenic sdLDL-cholesterol levels. This result might represent a new link between an atherogenic lipoprotein phenotype and innate immunity in T2DM. Further studies are needed to understand the mechanistic relationship between macrophage activation, small dense LDL, and their specific roles in atherosclerosis-related diseases.

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