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LIPID PROFILE AND SOLUBLE E-SELECTIN LEVELS DIFFERENCES BETWEEN TYPE 2 DIABETES MELLITUS OVERWEIGHT-OBESE AND UNDER-NORMOWEIGHT PATIENTS

PERBEDAAN PROFIL LIPID DAN KADAR SOLUBLE E-SELECTIN ANTARA PASIEN OVERWEIGHT-OBESE DAN UNDER-NORMOWEIGHT DENGAN DIABETES MELLITUS TIPE 2

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ABSTRAK

Diabetes melitus tipe-2 (DMT2) dan obesitas meningkatkan risiko dari penyakit arteri koroner sampai dengan 60-80%. Profil lipid merupakan salah satu dari petanda aterosklerosis dan dapat terganggu akibat resistensi insulin dan inflamasi yang terjadi pada pasien obesitas dengan DMT2. E-Selectin adalah molekul adhesi sel endotel yang dihasilkan dari aktivasi sel endotel yang rusak, dan mencerminkan perubahan struktur serta fungsional dinding pembuluh darah. Kadar soluble E-Selectin (sE-selectin) juga dapat berperan sebagai petanda disfungsi endotel Penelitian ini bertujuan untuk membuktikan adanya perbedaan profil lipid dan kadar sE-selectin pada pasien DMT2 overweight-obese dan under-normoweight. Penelitian ini menggunakan pendekatan belah lintang yang dilakukan pada 63 sampel antara Februari hingga Juni 2020, di Puskesmas X Semarang. Subjek DMT2 ditentukan berdasarkan diagnosis klinis. IMT dihitung dengan rumus, profil lipid diperiksa menggunakan metode enzimatik kolorimetrik, dan sE-selectin diperiksa menggunakan metode ELISA. Data dianalisis dengan program SPSS versi 22. Pada penelitian ini didapatkan perbedaan signifikan antara kadar kolesterol total, trigliserida, LDL, HDL, dan sE-selectin (p berturut-turut adalah 0,011; 0,043; 0,000; 0,008; 0,001) pada pasien DMT2 overweight-obese dibandingkan dengan under-normoweight. Dapat disimpulkan bahwa kadar kolesterol total, trigliserida, LDL, HDL, dan sE-selectin pada pasien DMT2 overweight-obese lebih tinggi dibandingkan under-normoweight.

Kata Kunci: *sE-selectin*, Profil lipid, Diabetes melitus tipe-2, Obesitas.

ABSTRACT

*Type-2 diabetes mellitus (T2DM) and obesity increase the risk of coronary artery disease by 60-80%. Lipid profile, one of the atherosclerosis markers, may be disrupted by insulin resistance and inflammation in diabetic obese patients. E-selectin is an adhesion molecule resulting from the activation of damaged endothelial cells and reflects the changes in the blood wall. Soluble E-Selectin (sE-selectin) level is also the marker of endothelial dysfunction. **T**his study aimed to determine differences in lipid profile and sE-selectin levels between T2DM overweight-obese and under-normoweight patients. This cross-sectional study was conducted on 63 samples since February to June 2020, at the X Community Health Center, Semarang. T2DM subjects were determined from clinicians' diagnoses. BMI was calculated with the formula, the lipid profile was examined using the colorimetric enzymatic method, and sE-selectin was examined using the ELISA method. Data were analyzed by SPSS program version 22. There were statistically significant differences in the levels of total cholesterol, triglycerides, LDL, HDL, and sE-selectin (p respectively 0.011; 0.043; 0.000; 0.008; 0.001) in T2DM overweight-obese and under-normoweight patients. In conclusion, higher total cholesterol, LDL cholesterol, triglyceride, E-selectin and lower HDL cholesterol are found in T2DM overweight-obese patients than T2DM under-normoweight patients.*

Keywords: *sE-selectin*, Lipid profile, Type-2 diabetes mellitus, Obesity.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic progressive metabolic disorder characterized by hyperglycemia due to absolute or relative deficiency in insulin secretion (WHO, 2019). *International Diabetic Federation* (IDF) reports that in 2019, 463 million (9.3%) individuals aged 20-79 years worldwide suffer from diabetes, and this number is estimated to increase to 578 million in 2030 and 700 million in 2045. In 2019 also, according to IDF, Indonesia is ranked 7th in the world with 10.7 million patients with diabetes (IDF, 2019). Of all kinds of diabetes, most cases were Type 2 Diabetes Mellitus (T2DM), which accounts for 90-95%. The highest proportion was in countries with low and moderate income (American Diabetes Association, 2020).

Obesity is another primary global health and economic problem. In 2016, more than 1.9 billion adults (39%) were overweight, and 650 million (13%) of them were obese (WHO, 2018). Obesity is defined as having a body mass index (BMI) of ≥27 according to Indonesian Basic Health Research *(Riset Kesehatan Dasar*) or BMI of ≥30 according to World Health Organization (Kementrian Kesehatan Republik Indonesia, 2018; WHO, 2004). Obesity is one of the main risk factor for diabetes, and 80% of T2DM patients are obese (Sharma *et al.*, 2016; Leitner *et al.*, 2017). Insulin resistance (IR), coagulation disorders, dyslipidemia, and cardiovascular complications are considered the most causes of morbidity and mortality in obese diabetic patients (Songa *et al.*, 2015; Al-Shreef and El-Kader, 2017). A significant increase in insulin resistance occurred in T2DM patients with obesity compared to T2DM patients without obesity (Tang *et al.*, 2019).

Dyslipidemia is a lipid profile disorder that often occurs in obese T2DM patients and is associated with the development of atherosclerosis. Insulin resistance and inflammation in T2DM, especially in obese patients increases the release of free fatty acids (FFA). Subsequently, this causes an increase in triglyceride (TG) levels and low-density lipoprotein (LDL) levels, and also causes a decrease in high-density lipoprotein (HDL) levels (Schofield *et al.*, 2016; Feingold and Grunfeld, 2018). These conditions lead to endothelial dysfunction, which plays a significant role as a triggering factor for the development of atherosclerosis and cardiovascular disease (Songa *et al.*, 2015; Ahmida *et al.*, 2017). Thus, diabetes mellitus patients have a higher risk of developing coronary heart disease (CHD).

Endothelial dysfunction occurs earlier before the development of cardiovascular disorders. There are various markers of endothelial dysfunction, which used to evaluate the risk of cardiovascular disease (Al-Shreef and El-Kader, 2017). The first morphological evidence of atherosclerosis is the adhesion of monocytes to the surface of endothelial cells. Monocytes adhere to the surface of cell adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). These markers could increase in T2DM patients. The mechanism may be related to the contribution of hyperglycemia, hyperinsulinemia, and insulin resistance (Matsumoto *et al.*¸ 2002).

E-selectin is an endothelial cell adhesion molecule that regulates the binding and extravasation of leukocytes from the bloodstream to sites of inflammation. Circulating form of E-selectin or soluble E-selectin (*sE-selectin*) results from damaged endothelial cells and reflects changes in the structure and function of blood vessel walls. The level of *sE-selectin* correlates with its expression on the surface of endothelial cells; hence, *sE-selectin* serves as a marker for endothelial dysfunction (Lee *et al.,* 2019*;* Qi *et al.*, 2010; El-Mesellamy *et al.*, 2012; Marsumoto *et al.,* 2010). E-selectin is only expressed on the activated endothelium, making it one of the most important adhesion molecules for the progression of atherosclerosis (Taniguchi *et al.*, 2005; Srivastava *et al.*, 2018).

Studies have reported high levels of *sE-selectin* in diabetes, hypertension, dyslipidemia, obesity, and smokers (Matsumoto *et al.*, 2010; Adamska *et al.,* 2014). Several studies stated increased levels of *sE-selectin* in obese T2DM patients, suggesting that E-selectin is an important independent factor associated with IR in T2DM patients without obesity (Taniguchi *et al.*, 2005). Obesity can induce endothelial activation or increased secretion of E-selectin in the cell surface, resulting in increased levels of *sE-selectin. SE-selectin* levels correlated with increased total fat volume, but not with regional fat distribution (Matsumoto *et al.*, 2002).

There are differences in studies' results related to lipid profiles in T2DM patients with and without obesity. Only a few studies analyzed the level of *sE-selectin* in T2DM patients with and without obesity. As far as our knowledge, currently, there are no studies that compared the lipid profile and *sE-selectin* in T2DM patients with and without obesity. Therefore, this study aims to determine the difference in lipid profiles

and *sE-selectin* levels between overweight-obese and under-normoweight T2DM patients.

MATERIALS AND METHODS

This cross-sectional study was conducted between February and June 2020 at Lebdosari Public Health Facility, Semarang, Indonesia. Inclusion criteria were individuals with T2DM for no more than ten years, aged 30-75 years, and blood pressure ≤ 120/80 mmHg. T2DM was diagnosed with fasting blood glucose level of ≥ 126 mg/dL. Subjects were divided into the overweight-obesity T2DM group (BMI ≥25) and T2DM under-normoweight T2DM group (BMI < 25). BMI ≥25 was chosen based on previous study which found significant lipid profile abnormality above this cut-off (Omoyote and Fadupin, 2016). Patients with a history of liver disease, heart disease, or malignancy; taking anti-dyslipidemia therapy; smokers and alcoholics; and women in the pregnancy or menstrual period were excluded from the study.

Data were collected from the medical record, interviewer-administered questionnaire, physical examination, and laboratory examinations. Data of age, gender, duration of diabetes, and history of other diseases were obtained by questionnaire. The weight and height of each patient were measured to calculate the body mass index (BMI). HbA1c levels were obtained from the patient's medical record.

Sixty-three subjects were included in the study, consisting of two groups, 34 patients of Overweight-obese T2DM and 29 patients of Under-normoweight T2DM. The characteristics of subjects in both groups were presented in Table 1. There were more female subjects in the Overweight-obese T2DM group, and the mean age was older in the Overweight-obese T2DM group. Blood pressure in both study groups was within normal ranges. The HbA1c value was higher in the obese group.

From each patient, laboratory tests were done to obtained lipid profile and *sE-selectin*. Ten ml venous blood sample was taken after 8-10 hours of fasting. Blood was allowed to settle for 30 minutes and underwent 1000 g centrifugation for 15 minutes. Serum was stored at -20^{o}C until further used. Lipid profiles including total cholesterol, HDL, LDL, and TG were measured by Cobas c501 analyzer (Roche, Germany). *SE-selectin* was analyzed using Abbexa Human E-Selectin ELISA Kit (abx050054, Abbexa, UK).

Statistical analysis was done using a SPSS for windows version 22. All data were presented as mean ± standard deviation or median with

minimum and maximum values as appropriate. The differences between the two groups were tested using the independent t-test and Mann-Whitney test. Significance was established based on a *p*-value <0.05. The study protocol was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Diponegoro University, Semarang, Indonesia with Ethical Research Clearance Certificate No. 34/EC/KEPK/FK-UNDIP/III/2020. Written and fully informed consent was obtained from all subjects before enrollment.

Table 1. Characteristics of Subjects

Variable	Overweight-obese T2DM	Under-normoweight T2DM	*p-value* (Mann-Whitney test)
	Median (min-max)	Median (min-max)	
Gender			
Male	10 (29.4%)	15 (51.7%)	
…Female	24 (70.6%)	14 (48.3%)	
Age (years)	61 (48-74)	60 (30-75)	0.415
BMI	21.73 (25.2-37.0)	22.22 (17.2-24.9)	0.000*
Systolic Blood Pressure (mmHg)	120 (100-120)	120 (90-120)	0.234
Diastolic Blood Pressure (mmHg)	70 (60-80)	70 (50-70)	0.910
HbA1c (%)	8.1 (5.5-14.2)	7.4 (5-15.3)	0.151

*significant (*p-value* <0.05); T2DM, Type 2 Diabetes Mellitus; SD, standard deviation; min, minimum; max, maximum.

Table 2. Differences in Lipid Profiles and *sE-selectin* among the Overweight-obese T2DM Group and Under-normoweight T2DM Group

Variable	Overweight-obese T2DM		Under-normoweight T2DM		*p-value*
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Total Cholesterol (mg/dL)	223.88 ± 38.97		200.41 ± 30.82		0.011†*
Triglyceride (mg/dL)		178 (87-325)		123 (52-240)	0.043ᴍ*
LDL (mg/dL)	158.9 ± 31.73		132.45 ± 21.51		0.000†*
HDL (mg/dL)	41 ± 6.35		46 ± 8.32		0.008†*
sE-selectin (ng/mL)		100.99 (2.07-305.4)		43.27 (0.59-172.5)	0.001ᴍ*

T2DM, Type 2 Diabetes Mellitus; SD, standard deviation; min, minimum; max, maximum; LDL, low-density lipoprotein; HDL, high-density lipoprotein; *sE-selectin*, soluble E-selectin; *significant (*p-value* <0.05); ᴍ Mann Whitney; † independent t-test.

RESULTS AND DISCUSSION

In this study, more females were found in overweight-obese T2DM group. Moreover, the median age of females in overweight-obese T2DM group was higher than under-normoweight T2DM group. Menopause is associated with a faster increase in fat mass and redistribution of fat to the abdomen, resulting in a transition from gynaecoid to android fat distribution pattern and increasing overall total body fat. Postmenopausal women have a higher amount of intra-abdominal fat than premenopausal women (Davis *et al.*, 2012).

Patients in the overweight-obese T2DM group tended to be older than in the Under-normoweight T2DM group. The aging process in

T2DM patients leads to increased glucose intolerance, decreased ability of pancreatic beta cells to produce insulin, decreased body metabolism, decreased physical activity, and altered the patient's diet and adherence in taking anti-diabetic drugs. All of which can affect BMI (Mooradian *et al.*, 2004). The HbA1c levels in the Overweight-obese T2DM group were higher than in the Under-normoweight T2DM group and categorized as poor glycemic control (HbA1c >8%). This result indicates that uncontrolled accumulation of blood sugar levels may increase the risk of obesity (Putri and Larasati, 2013; Suciwati *et al.*, 2019).

Table 2 presented the differences in lipid profiles and *sE-selectin* levels among the Overweight-obese T2DM group and Under-normoweight T2DM group. Mean total cholesterol, triglyceride, and LDL level in the Overweight-obese T2DM group was higher than in the Under-normoweight T2DM group ($p = 0.011$, $p = 0.043$, $p < 0.001$, respectively). Otherwise, HDL level was lower in the Overweight-obese T2DM group ($p = 0.008$) (Figure 1). *SE-selectin* levels were higher in the Overweight-obese T2DM group than in the Under-normoweight T2DM group ($p = 0.001$) (Figure 1).

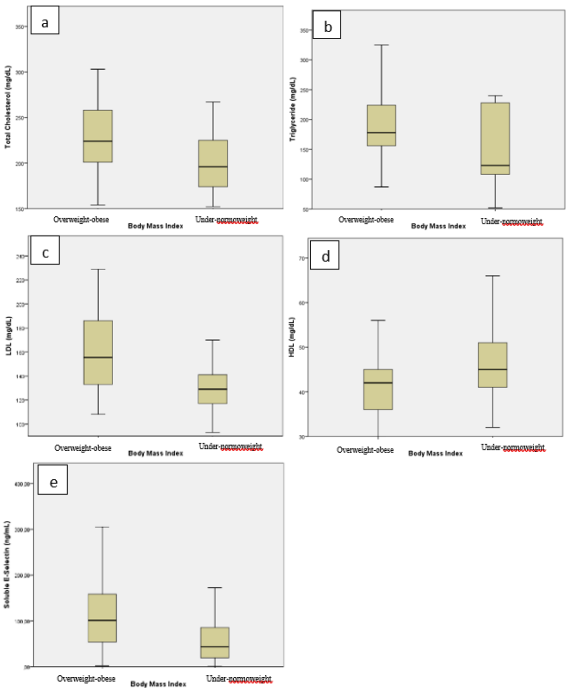

Figure 1. Box-plot graphs of differences in lipid profile and *sE-selectin* levels in T2DM overweight-obese and under-normoweight patients. Mean total cholesterol (a), triglyceride (b), and LDL level (c) in the overweight-obese T2DM group was higher than in the under-normoweight T2DM group; $p = 0.011$, $p = 0.043$, $p < 0.001$. HDL level (d) was lower in the Overweight-obese T2DM group ($p = 0.008$). sE-selectin levels (e) were higher in the Overweight-obese T2DM group than in the Under-normoweight T2DM group ($p = 0.001$). T2DM, type 2 diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein; *sE-selectin*, soluble E-selectin.

This study reveals that the total cholesterol, triglyceride, and LDL levels in the Overweight-obese T2DM group were higher than those in the Under-normoweight T2DM group. On the contrary, HDL levels in the Overweight-obese T2DM group were lower than those in the Under-normoweight T2DM group. This result is in line with the previous studies conducted in 2014 and 2016, which showed a significant difference in lipid profile levels in the T2DM

with and without obesity (Cantika, 2014; Omoyote and Fadupin, 2016). Another study in 2017 also showed that cholesterol and triglyceride levels were significantly higher in the obese diabetes group than in the non-obese diabetes group in both men and women; however, LDL and HDL levels were only significantly different in men (Ahmida *et al.*, 2017).

The median lipid profile in the Overweight-obese T2DM group in our study (total cholesterol 224 mg/dl, triglycerides 178 mg/dl, LDL 155.5 mg/dl, and HDL 42 mg/dl) was in accordance with NCEP ATP III criteria for dyslipidemia. Dyslipidemia occurs more frequently in the T2DM with obesity group than in the T2DM without obesity group (Budiman *et al.*, 2015). This phenomenon is related to the insulin resistance, which is the main pathogenesis of hyperglycemia and dyslipidemia in obese T2DM subjects. Insulin resistance and inflammation in T2DM and obesity increase the release of FFAs, which leads to increased LDL levels (Schofield *et al.*, 2016; Feingold and Grunfeld, 2018; Ahmida *et al.*, 2017).

Obesity and T2DM are associated with increased triglyceride deposits in non-adipose tissues, such as the heart, liver, pancreas, and skeletal muscle; increased production of VLDL particles in the liver; and decreased clearance of triglyceride-rich lipoproteins (Yadav *et al.*, 2012). Excess visceral fat in obesity is associated with increased triglyceride metabolism. The increased secretion of VLDL in the liver is associated with hepatic steatosis and increased visceral adiposity. In addition, impaired clearance of triglyceride-rich VLDL lipoproteins and increased apolipoprotein C-III (apo C-III), which is the main regulator of triglyceride metabolism, caused central obesity-related hypertriglyceridemia (Bjornson *et al.*, 2017).

Our subjects in Overweight-obese T2DM group had worse glycemic control and tended to be older. Therefore, their serum HDL levels tend to be lower. Low serum HDL levels are associated with an increased clearance fraction of HDL secondary to cholesterol depletion in obesity (Yadav *et al.*, 2012; Wahab *et al.*, 2014). Hyperglycemia increased hepatic lipase's activity, leading to increased fractional clearance of HDL. It also impaired VLDL catabolism leads to decreased HDL formation (Mamatha *et al.*, 2015).

Dyslipidemia that occurred in obese patients with T2DM could have another implication. Free fatty acids and intermediate lipids activate protein kinase, which

phosphorylates and inhibits the PI3K insulin pathway and stimulates ROS production. Increased ROS causes oxidative stress and decreases NO levels, causing endothelial dysfunction which leads to increased levels of *sE-selectin (*Srivastava *et al.*, 2018; Suciwati *et al.*, 2019).

The present study showed that the level of *sE-selectin* in the Overweight-obese T2DM group was higher than the Under-normoweight T2DM group. This is similar with the previous study in 2002, which stated diverse levels of *sE-selectin* in the T2DM with and without obesity group (Matsumoto *et al.*, 2002). A previous study conducted by Adamska *et al.*. (2012) showed that the concentration of *sE-selectin* differed significantly in obese women compared to those without obesity, and another study by El-Mesallamy *et al.*, (2012) showed that the concentration of *sE-selectin* was significantly different in obese T2DM patients with CHD compared to healthy controls (Adamska *et al.*, 2012; El-Mesellamy *et al.*, 2012).

The earliest morphological evidence of atherosclerosis is the adhesion of monocytes to the surface of endothelial cells. Monocytes will attach to the surface of cell adhesion molecules such as *E-selectin*. *E-selectin* is the most important adhesion molecule for the development of atherosclerosis because it is expressed exclusively on the activated endothelium. Increased *sE-selectin* is a predictor of vascular events in T2DM patients (Matsumoto *et al.*, 2002; Taniguchi *et al.*, 2005; Srivastava *et al.*, 2018).

Endothelial dysfunction in T2DM and obesity occurs through hyperglycemia, insulin resistance, and inflammation. The levels of *sE-selectin* are higher in the Overweight-obese T2DM group, seemingly due to inflamed adipose tissues in this group. The inflamed tissues release large amounts of FFA, lipid intermediate metabolites (DAG and ceramide), and inflammatory cytokines. Entirely, this process inhibits the production of anti-inflammatory adipokines such as adiponectin. Adiponectin is an adipocyte-specific secretory protein and inhibits the expression of adhesion molecules on aortic endothelial cells. In endothelial cells, adiponectin increases NO production and suppresses oxidative stress and inflammatory signaling cascades, reduces monocyte adhesion to endothelial cells, and inhibits expression of adhesion molecules. Another possibility that causes an increase in *sE-selectin* levels in obesity is the release of *E-selectin*, which is more

sensitive to fat-derived mediators (Ahmida *et al.*, 2017; Matsumoto *et al.*, 2002; Lukich *et al.*, 2014; Oever *et al.*, 2010).

There are several limitations to this study. The researchers did not measure whether the patient consumed high-cholesterol and high-triglyceride foods, which might affect the lipid profile. The exclusion screening for a history of liver disease, cardiac disease, and malignancy that may affect *sE-selectin* levels was obtained entirely by questionnaire. Future studies should also involve checking AST and ALT levels to rule out systemic diseases that could affect *sE-selectin* levels.

CONCLUSION

Overweight-obese T2DM is associated with higher total cholesterol, triglycerides, LDL cholesterol, *sE-selectin*, and lower HDL cholesterol.

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