Correlation between HbA1c and Triglyceride Level with Coronary Stenosis Degree in Type 2 Diabetes Mellitus with Coronary Heart Disease

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Abstract

BACKGROUND: The mortality of coronary heart disease (CHD) in type 2 diabetes mellitus (DM) increased 2–4 times more than non-diabetics because of coronary stenosis. One of the risk factors for CHD in type 2 DM is dyslipidemia. Hypertriglyceridemia plays an important role in atherosclerosis coronary arteries theoretically.

AIM: This study analyzed the parameters of HbA1c and triglyceride levels with the stenosis severity of coronary artery that occurs in type 2 DM patients with CHD that has not been analyzed so far.

METHODS: This study was a cross-sectional observational analytic study. Forty patients of type 2 DM with CHD in Kariadi Hospital on September 2013 were recruited based on the inclusion and exclusion criteria. HbA1c level in plasma was measured by turbidimetric immunoassay method. Triglyceride level was measured by enzymatic methods. Coronary stenosis was based on coronary angiography result as percentage. Spearman correlation test was used and p < 0.05 was considered statistically significant.

RESULTS: Mean HbA1c and triglyceride levels were 8.89 ± 1.498 % and 220.97 ± 92.24 mg/dL. The correlation test between HbA1c and triglycerides (TG) level with coronary stenosis, respectively, was p = 0.002, r = 0.466; p < 0.001, r = 0.665.

CONCLUSION: HbA1c and triglyceride levels increase in line with the increasing stenosis severity of coronary heart disease in patients with type 2 DM.

Introduction

Diabetes mellitus (DM) is a chronic degenerative disease with a prevalence that continues to increase from year to year [1]. DM is a group of metabolic diseases with characteristics of chronic hyperglycemia due to defects in insulin secretion, insulin work, or both [2, 3]. A study by Shaw showed that the prevalence of diabetes worldwide in the adult population aged 20–79 years was 6.4% in 2010, affected 287 million adults and was expected to increase to 7.7%, and will affect 439 million adults by 2030. The prevalence of DM in Indonesia in 2010 was estimated at 4.6% with the number of patients as many as 6,964,000 patients [4]. Type 2 diabetes is also known as adult type or non-dependent insulin type [5], [6]. The World Health Organization (WHO) predicts an increase in the number of DM patients in the next years, especially in Indonesia. The WHO predicted an increase in the number of patients from 8.4 million in 2000 to ± 21.3 million in 2030 [3].

Pathogenesis of type 2 DM is based on impaired insulin secretion by pancreatic beta cells and insulin work disorders due to insensitivity (resistance) of target tissue to insulin. The main cause of death in type 2 DM is coronary heart disease (CHD) of approximately 80% as a complication of DM [7], [8]. The mortality rate of CHD in patients with type 2 diabetes can increase 2–4 times more than those who are non-diabetic due to atherosclerotic lesions in people with type 2 diabetes, which makes the development process is faster [7], [8], [9], [10].

CHD, often called ischemic heart disease, is most often caused by atheroma plaque blockage (atherosclerosis) in the coronary arteries. Atherosclerosis causes narrowing of the coronary artery lumen (coronary stenosis/coronary artery stenosis), so the blood flow to the myocardial is disrupted and results in myocardial ischemia. When the plaque ruptures, a thrombosis process occurs. This series of events gives clinical manifestations ranging from stable angina pectoris to sudden death. Diagnostic tests to see the cause of CHD are obtained from invasive coronary angiography performed at cardiac catheterization. Invasive coronary angiography is used to determine the presence of coronary stenosis lesions (coronary arteries) in the heart and to know the extent of
stenois which is the cause of CHD. The current invasive coronary angiography is a routine examination for the diagnosis of coronary artery disease (CAD), which is significant if stenosis is >50% in lumen diameter [11].

The development of atherosclerosis occurs gradually, and the process is complex, which is caused by interactions between risk factors, endothelial cell dysfunction, lipid oxidation, and lipid accumulation [12], [13]. One of the risk factors for CHD in type 2 DM is dyslipidemia. Diabetic dyslipidemia has characteristics of hypertriglyceridemia (HTG), increased very low density lipoprotein (VLDL), and small dense LDL [14], [15]. The role of triglycerides (TGs) as a risk factor for CHD has long been studied but until now it has not been determined whether TG increases are independent risk factors of CHD. Studies showed that an increase in the metabolism of triglyceride-rich lipoprotein (TGLRP) was important in the pathogenesis of atherosclerosis and could predict the presence of CHD. There is evidence that TGLRP has a pathologic role in possible atherothrombosis due to the endothelial damage [16]. High triglyceride levels in DM are caused by hyperglycemia as a manifestation of impaired carbohydrate metabolism, which, if it is not addressed immediately, will be followed by disorders of fat metabolism or dyslipidemia [17]. Diabetic dyslipidemia is a condition which is characterized by high levels of TG and cholesterol caused by diabetes, especially uncontrolled diabetes [14].

It has been widely known that type 2 DM has a relationship with the degree of hyperglycemia, an increased risk of mortality from microvascular complications, myocardial infarction, and macrovascular complications based on the previous studies [7], [18]. The process of coronary stenosis is an long process, occurring from a young age and developing for a long life. According to Diabetes Control and Complications Trial, variations in glucose profiles for several days cannot predict diabetes complications [18]. Glycosylated hemoglobin levels (HbA1c) can be predictors of CHD in DM patients and it is reported that good glucose control is associated with reduced risk of CHD. Reported increases in HbA1c levels are associated with an increased risk of CHD independently [19].

The study of Lee et al. concluded that patients with type 2 DM with high HbA1c variability could be an independent predictor of CAD with an average HbA1c level of more than 7% [18]. The study of Ertem et al. stated that there was no significant relationship between severity of CAD with HbA1c in patients with non-diabetic ACS [20]. The study of Yan et al., assessing the relationship of lipid and HbA1c ratio in type 2 DM, concluded that there was no relationship between HbA1c and TG or HDL [21]. Petitti et al. in their study showed that there was a relationship between high HbA1c level and an increase in TG [22].

Existing study showed that HbA1c had a role in DM patients with CHD as well as HTG also played a role in the process of forming atherosclerosis in blockage of coronary arteries. This study analyzed the parameters of HbA1c and triglyceride levels with the stenosis severity of coronary artery that occurs in type 2 DM patients with CHD that has not been analyzed so far.

**Methods**

This study was an observational analytic study with cross-sectional approach conducted at Dr. Kariadi Central Hospital, Semarang, Indonesia, during September 2013. It had been approved by the Health Research Ethics committee of Faculty of Medicine, Diponegoro University/Dr. Kariadi Central Hospital, Semarang, number 415/EC/FK/RSDK/2013. All study subjects were requested to give written informed consent and patient's identity was confidential.

The subjects were 40 patients with type 2 DM with complications of CHD who received cardiac catheterization. CHD was diagnosed by a cardiologist based on a physical examination, an electrocardiogram, heart laboratory test, and a treadmill test.

The inclusion criteria were those over 20 years old, underwent cardiac catheterization, and willing to take part in the study, while the exclusion criteria were having hemoglobin abnormalities and taking regular dyslipidemia drugs.

The respondent’s identity, smoking history, and physical examination were collected, and the respondents were taken for middle cubital venous blood as much as 3 cc of ethylenediaminetetraacetic acid (EDTA) blood and 3 cc in a plain tube. EDTA blood was immediately homogenized and HbA1c levels were then examined, while plain tubes were left for 30 min to get the serum and were then centrifuged with the speed of 3000 rpm for 5 min, then the serum was examined for the triglyceride levels in the laboratory of Dr. Kariadi Central Hospital. Plasma HbA1c levels, assessed by the turbidimetric immunoassay method (equipment, manufacturer, and country), were expressed as a percentage. Serum triglyceride levels were assessed by enzymatic method (equipment, manufacturer, and country), expressed in mg/dL. Subjects underwent cardiac catheterization to see the degree of stenosis of the coronary arteries by the cardiologist which was expressed in percentages then classified as stenosis if the heart block was more than 50%, non-significant stenosis if the heart block was <50%, and no stenosis if there was 0% blockage.

The collected data were in the form of interviews, physical examination, and laboratory examination. The collected data were edited, coded, and incorporated into computer programs. Bivariate statistical analysis was done using the Pearson relationship test. The significance level was p <0.05.
Results

The average age of the subjects was 56.05 years with a standard deviation of 9.2 years. The sex of the study subjects was mostly male. The mean body mass index (BMI) value with the standard deviation of the study subjects was 24.88 ± 3.446 kg/m². Based on the BMI value for Asians, most of the study subjects were classified as obese. The characteristics of subject are present in Table 1.

Table 1: The characteristics of study subjects

| Characteristics | n (%) |
|-----------------|-------|
| Sex             |       |
| Male            | 29 (72.5) |
| Female          | 11 (27.5) |
| Age (years), mean ± SD | 56.05 ± 9.21 |
| BW (kg), mean ± SD | 65.97 ± 9.84 |
| BH (cm), mean ± SD | 162.77 ± 6.49 |
| BMI (kg/m²), mean ± SD | 24.88 ± 3.44 |
| Underweight     | 1 (2.5)  |
| Normal          | 9 (22.5) |
| Pre-obese       | 14 (35.0) |
| Obese           | 16 (40.0) |

The overall HbA1c levels of respondents in this study increased above normal. Respondents with a significant degree of stenosis had the highest HbA1c level compared with neither non-significant stenosis nor stenosis. The same situation occurred in triglyceride parameters where respondents with significant stenosis had the highest triglyceride levels (Table 2).

Table 2: The mean glycosylated hemoglobin and triglyceride levels based on stenosis severity of coronary artery in patients with type 2 diabetes mellitus and coronary heart disease

| Stenosis severity (%) | HbA1c level (%) | TG level (mg/dl) |
|-----------------------|-----------------|-----------------|
| No stenosis           | 6.31 ± 1.303    | 128.00 ± 55.07  |
| Non-significant stenosis | 6.90 ± 0.458    | 126.00 ± 49.93  |
| Stenosis              | 8.89 ± 1.498    | 220.97 ± 92.24  |

The analysis result of the relationship test (Tables 3 and 4) showed that both HbA1c and triglyceride levels were significantly associated with the degree of stenosis in patients with type two DM with complications of CHD.

Discussion

The results of the relationship test between HbA1c and coronary stenosis showed a strong positive relationship. This was in accordance with the study of Saleem et al. and Su et al. who concluded that there was a positive relationship between coronary stenosis and HbA1c [9], [23]. A study by Rivera et al. also concluded that the increased HbA1c level was related to the presence of coronary stenosis but in the non-DM population [24]. The role of glucose variability in the pathogenesis of atherosclerosis remains unclear.

Table 3: The relationship between glycosylated hemoglobin and triglyceride levels and stenosis severity of coronary artery disease in patients with type 2 diabetes mellitus and coronary heart disease

| Parameter              | Stenosis severity (%) | r     | p       |
|------------------------|-----------------------|-------|---------|
| HbA1c level (%)        |                       | 0.665 | < 0.001 |
| TG level (mg/dl)       |                       | 0.501 | 0.001   |

Hyperglycemia is thought to induce oxidative stress and interfere with endothelial cell function by overproduction of reactive oxygen species (ROS), which results in coronary stenosis through several molecular mechanisms. In vitro studies showed that blood glucose fluctuations could activate nuclear factor-κB and protein kinase C (PKC) pathways, which result in excessive expression of adhesion molecules and formation of advanced glycation end-products [25], [26]. Several studies have shown that apoptosis in endothelial cells intermittently exposed to high blood glucose may be related to overproduction of ROS, through PKC-dependent activation of nicotinamide adenine dinucleotide phosphate oxidase and apoptosis through activation of the caspase cascade resulting in cell death due to its binding with the ligand, which will result in coronary stenosis through endothelial dysfunction [26], [27], [28].

Table 4: The relationship between glycosylated hemoglobin level and triglyceride level in patients with type 2 diabetes mellitus and coronary heart disease

| Parameter              | TG level (mg/dl) | r     | p       |
|------------------------|-----------------|-------|---------|
| HbA1c level (%)        | 0.665           | 0.466 | 0.002   |

The result of the relationship test between TG and coronary stenosis showed a moderate positive relationship. Some previous studies have not directly linked TG with coronary stenosis, but several recent studies have suggested that the increase in TG is independently related to the incidence of CHD. The Copenhagen male study at 8 years of follow-up reported that an increase in fasting TG was a strong independent risk factor for CHD [29], [30].

Increased plasma TG and TGLRP are risk factors for atherothrombosis. Some TGLRP can cause endothelial dysfunction that can potentially trigger atherothrombosis, including chylomicron from normal individuals as well as individuals with hyperlipoproteinemia and VLDL from individuals with elevated TG/HTG (HTG-VLDL). Endothelial cells bind and enter TGLRP from individuals with HTG with the effect of deterioration including a decrease in fibrinolytic capacity. HTG-VLDL inhibits plasminogen binding in endothelial cells and modulates PAI-1 release, thereby inhibiting plasmin formation [31]. Reaven suggested the existence of an insulin resistance syndrome wherein cardiovascular risk occurs more frequently. Insulin, pro-insulin like molecules, glucose, and VLDL TG directly stimulate transcription and secretion of PAI-1 in endothelial cells [32], [33], [34], [35].
The results of the Spearman test for the relationship between HbA1c and TG were found to be a moderate positive relationship. This was different from the results of the study of Yan et al. who concluded that there was no correlation between HbA1c and TG [21]. However, according to the study of Pettiti et al., there was a significant relationship between elevated triglyceride levels and increased HbA1c levels in DM population [22]. High triglyceride levels in type 2 DM caused by hyperglycemia which was a manifestation of impaired carbohydrate metabolism. Various metabolic disorders found in T2DM or in insulin resistance syndromes such as hyperglycemia which lead to atherosclerosis and dyslipidemia. Insulin resistance associated with type 2 diabetes has several effects on fat metabolism. In a state of insulin resistance, the sensitive hormone lipase in the adipose tissue will become active so that lipolysis of TG in the adipose tissue will increase, and this condition will produce excessive free fatty acids. Some free fatty acids will be taken to the liver as a raw material for forming TG. The state of insulin resistance, in the liver, will produce VLDL which is rich in TG [17].

This study did not analyze the study variables based on the characteristics of the respondents, especially the BMI. In addition, this study did not exclude comorbid disease from DM, namely, hypertension, and did not take into account the condition of patients who had undergone therapy for the complaints of heart disease or therapy for abnormal metabolic fat.

Conclusion

HbA1c and triglyceride levels increased in line with the increasing stenosis severity of CHD in patients with type 2 DM. These two parameters can be used as markers to evaluate patients with DM who can experience significant blockages and develop toward more severe heart disease.

Acknowledgments

We thank to laboratory technician of Dr. Kariadi Public Hospital for running the laboratory examination. We also thank to cardiologist of Dr. Kariadi Public Hospital for determining the stenosis degree of subject.

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