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Original Article

New-onset type 2 DM risk in dyslipidemia and stroke patients due to simvastatin use

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ABSTRACT

Simvastatin is a therapy management for dyslipidemia and stroke, which are prevalent in Indonesia. These drugs are very effective in reducing the incidence of cardiovascular disease and mortality in high-risk patients. However, long-term use of simvastatin may lead to new problems, such as the risk of new-onset type 2 DM. This study aims to monitor the blood glucose profile to determine the risk of new-onset type 2 DM. This study is observational with a prospective one-group pre-test and post-test design conducted at the outpatient polyclinic of UNISMA Islamic Hospital Malang from February to June 2018. The sample consisted of patients who received a long-term simvastatin therapy dose of 20 mg. A paired t-test was performed when the data were normally distributed to determine the significance of FPG and HbA1c levels changes. The results showed that the increase in fasting plasma glucose (FPG) levels at the first and third months was not statistically significant (97.44 mg/dL vs. 100.33 mg/dL; p = 0.196). Similarly, the increase in HbA1c levels was not statistically significant (6.79% vs. 7.53%; p = 0.076). However, the results of FPG and HbA1c showed that all patients (27 people) have the possibility of experiencing new-onset type 2 DM. In short, routine intake of 20 mg simvastatin with a minimum usage duration of 6 months has caused 27 patients to experience a new-onset type 2 DM.

Keywords: Dyslipidemia, HbA1c, New-onset Type 2 DM, Simvastatin, Stroke

Introduction

Currently, there is an epidemiological change in Indonesia, particularly the epidemics of non-communicable diseases, such as dyslipidemia and stroke. Lifestyle and nutrition transitions have led to many disease pattern changes in society [1-3]. Dyslipidemia is a disorder of lipid metabolism characterized by increasing or decreasing plasma lipid fraction. The primary abnormalities are the increasing levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides (TG), as well as the decreasing level of high-density lipoprotein (HDL) [4]. Further, this disease is caused by lipid metabolism disruption due to genetic and environmental factors, and it becomes one of the risk factors of stroke [5, 6]. Generally, stroke, which attacks the brain, occurs suddenly, progressively, and quickly because of local and/or global disruption of nerve function [7]. As a serious disease, the prevalence of stroke in Indonesia increased from 7‰ in 2013 to 10.9‰ in 2018 [8].

Proper management of a dyslipidemia condition is necessary to prevent cardiovascular diseases, such as stroke. Pharmacological therapies for dyslipidemia are statins, PCSK9 inhibitors, bile acid sequestrants, omega-3 fatty acids, cholesterol absorption inhibitors, niacin, and fibrates. The choice of hypolipidemic drug class depends on the lipid effects after examining the patient's LDL, HDL, and TG levels [1, 9, 10]. The most widely prescribed hypolipidemic drugs in Indonesia are statins, such as simvastatin 10 mg (low-intensity Statin), simvastatin 20 mg (moderate-intensity Statin), and atorvastatin 40 mg (high-intensity Statin). The statin class effectively reduces the incidence of cardiovascular disease and mortality in high-risk patients. However, apart from their ability to lower LDL, statins also have

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pleiotropic effects, such as improving endothelial function and reducing inflammation and thrombus formation. O'Brien *et al.* reported the benefits of statins on ischemic stroke patients in the form of reduced cardiovascular risk [11-14]. Currently, statin therapy is widely recommended for primary and secondary preventions of cardiovascular disease with various conditions. The benefit is related to its pleiotropic effect, which does not depend on Statin's ability to reduce LDL levels [11, 14].

Despite their benefits, statin drugs may cause new problems, such as type 2 diabetes mellitus (DM) risk due to long-term use. On February 28, 2012, the United States Food and Drug Administration (FDA) updated information on statins after providing recommendations for monitoring liver function and reports of memory loss. The FDA also warned against the possibility of the new-onset type 2 DM and worsening blood glucose control in patients given statins [15]. Many reports of clinical evidence showed that statins increase the risk of new-onset type 2 DM. These statins include atorvastatin, simvastatin, lovastatin, fluvastatin, and pitavastatin, which significantly increase the new-onset type 2 DM risk [16-18]. Prolonged use of statins without blood sugar monitoring can expose patients to increased morbidity and mortality problems. Therefore, research is needed to monitor the side effects of statin drugs associated with fasting blood glucose and HbA1c to prevent the new-onset type 2 DM.

Materials and Methods

Study design

This is an observational study with a prospective one-group pre-test post-test design on patients given simvastatin. This study was conducted at the outpatient polyclinic of UNISMA Islamic Hospital, Malang City, from February to June 2018. The research design was approved by the Ethical Commission for Health Research, Faculty of Medicine, Universitas Brawijaya through the ethical approval letter number 450/EC/KEPK/12/2017.

Study population and samples

The sample was patients who fulfilled the inclusion criteria, namely 1) Outpatients routinely taking simvastatin drugs; 2) Patients aged ≥50 years; 3) Patients with a diagnosis of dyslipidemia and/or stroke; 4) Patients given simvastatin for at least six months; and 5) Patients who willingly signed the informed consent. Meanwhile, the exclusion criteria were 1) Patients who smoke; 2) Patients who consume alcohol; 3) Patients with a history of type 2 diabetes mellitus; 4) Patients taking other drugs that could increase blood glucose levels, such as corticosteroid, antidepressants, and adrenaline drugs; 5) Patients without complete medical record data; 6) Patients with decreasing adherence in taking simvastatin during the study period; and 7) Patients who experienced severe muscle pain due to the simvastatin usage and became "on-off" in taking the drugs.

Data collection

Subject recruitment was done using a consecutive sampling method conducted when the patients visited the physicians for a routine check-up. The patients signed the consent form to show their willingness to participate in the study. Further, a fasting schedule before FPG and HbA1c examinations was conducted. The assessment of these two parameters was completed in the laboratory where this study was conducted. The FPG and HbA1c levels were examined twice in the first and the third months since the patients were recruited in the study.

Data analysis

Numerical data were presented in decimal form with the center trend of mean ± SD (Standard Deviation) when the data is usually distributed. However, the categorized patient data were processed in proportion and presented in tables and figures.

FPG and HbA1c level changes were analyzed by comparing the examination results during the first and third months. A data normality test was conducted using the Shapiro-Wilk analysis. Further, to determine the significance of the changes in FPG and HbA1c levels, a paired t-test was performed when the data were normally distributed. In contrast, the Wilcoxon test was used to determine the significant changes when the data were not normally distributed. The p-value <0.05 showed that the FPG and HbA1c levels in the first month were statistically different from those in the third month.

Results and Discussion

In this study, 27 patients participated and were willingly available for three months from the initial enrollment until the study completion. All patients signed the informed consent form, and they were able to complete the study.

Table 1. Characteristics of Research Subjects

Characteristics	Mean ± SD (N = 27)	Proportion n (%) (N = 27)
Age (years)	60.93 ± 6.64	
The usage duration of simvastatin 20 mg (months)	13.74 ± 9.72	
Age group		
50 – 59 years old		11 (40.74)
60 – 69 years old		11 (40.74)
70 – 79 years old		5 (18.52)
Gender		
Male		16 (59.26)
Female		11 (40.74)
Comorbid*		
Hypertension		14 (51.85)
Dyslipidemia		5 (18.52)
Low back pain		1 (3.70)
Stroke		12 (44.44)
Cardiomegaly		1 (3.70)
Heart failure		3 (11.11)
Atrial fibrillation		1 (3.70)
Hyperthyroidism		1 (3.70)

The usage duration of simvastatin 20 mg	
6 – 11 months	16 (59.26)
12 – 24 months	7 (25.93)
25 – 39 months	4 (14.81)
DM criteria based on the GDP level in the 1st month	
Normal (Not DM)	18 (66.67)
Pre-diabetes (Uncertain DM)	8 (29.63)
DM	1 (3.70)
DM criteria based on the GDP level in the 3rd month	
Normal (Not DM)	16 (59.26)
Pre-diabetes (Uncertain DM)	9 (33.33)
DM	2 (7.41)
DM criteria based on the HbA1c level in the 1st month	
Normal (Not DM)	0 (0.00)
Pre-diabetes (Uncertain DM)	14 (51.85)
DM	13 (48.15)
DM criteria based on the HbA1c level in the 3rd month	
Normal (Not DM)	1 (3.70)
Pre-diabetes (Uncertain DM)	11 (40.74)
DM	15 (55.56)

Note:

*One patient can suffer from more than one comorbid. The comorbid proportion (%) is calculated from the number of comorbid patients divided by the total subject (27 patients).

Normal: FPG level 70-99 mg/dL and/or serum HbA1c level <5.7% [19, 20]

Pre-diabetes: FPG level at 100-125 mg/dL and/or serum HbA1c level at 5.7-6.4% [19, 20]

Diabetes: FPG level ≥ 126 mg/dL and/or serum HbA1c level ≥6.5% [19, 20]

The characteristics of the patients are presented in **Table 1**. In this study, the number of males (59.26%) is higher than females. Most of the patients (59.26%) are in the elderly category, between 60 and 79 years old. The most common disease among patients is hypertension (51.85%). Most of the patients (59.26%) take simvastatin 20 mg within 6 to 11 months. The FPG level examination in the first month showed that most patients (66.67%) did not experience DM. Similarly, in the third month (59.26%), most patients did not experience DM. However, the proportion of patients who did not experience DM in the third month was lower than in the first month. It is because one patient experienced a pre-diabetes condition, while others experienced DM in the third month. Meanwhile, the HbA1c level examination in the first month showed that most of the patients (51.85%) had pre-diabetes, while others (55.56%) experienced DM in the third month. The average values of FPG levels in the first and third months are shown in **Figure 1**, while the average values of HbA1c levels are shown in **Figure 2**.

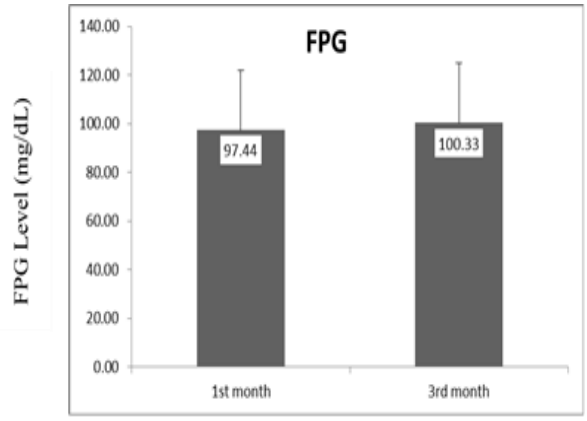

Figure 1. Mean of FPG Level at the 1st and 3rd Months (p = 0.196).

*Result is statistically significant if p-value < 0.05.

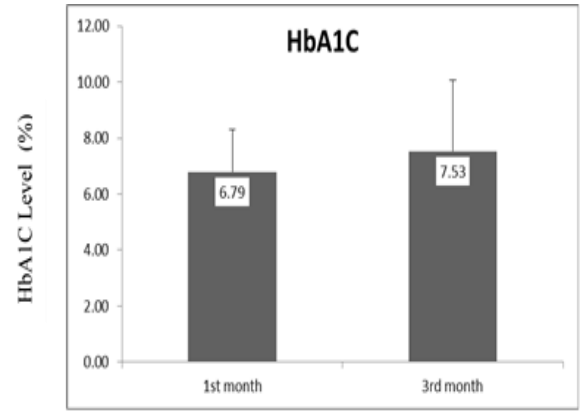

Figure 2. Mean of HbA1c Level at the 1st and 3rd Months (p = 0.076).

*Result is statistically significant if p-value < 0.05.

The examination results showed increasing fasting plasma glucose levels among 15 patients (55.56%) during the third month **(Figure 3)**; meanwhile, there were increasing HbA1c levels in 16 patients (59.26%) **(Figure 4)**.

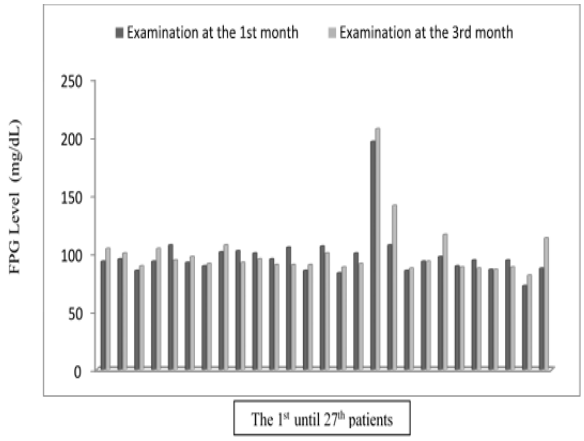

Figure 3. FPG Level in Each Patient

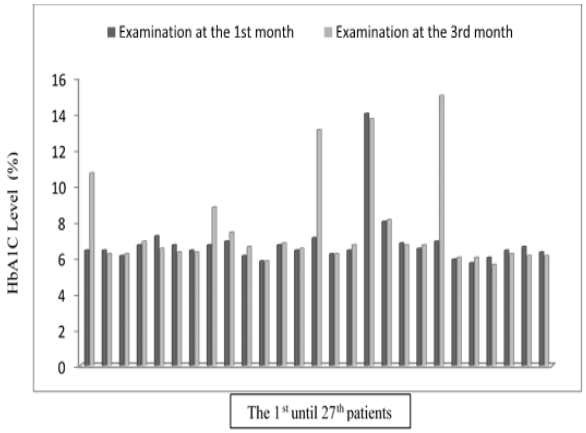

Figure 4. HbA1c Level in Each Patient

The category determination for the DM diagnosis is based on the results of FPG and HbA1c examinations during the first and third months since the patient recruitment. **Table 2** shows that all patients in this study were possible to experience the new-onset type 2 DM. There was no patient with a normal category either in the first or third month; but, there was a patient (code 24) in a normal category in the third month, although his examination results in the first month were in the pre-diabetes category. Therefore, the patient was included in the category of people affected by new-onset type 2 DM.

Table 2. Patient Identification with New-onset Type 2 DM

Patient Number	DM Diagnosis Category		Conclusion
	1st Month	3rd Month	
1.	Pre-diabetes	Diabetes	+
2.	Pre-diabetes	Pre-diabetes	+
3.	Pre-diabetes	Pre-diabetes	+
4.	Diabetes	Diabetes	+
5.	Diabetes	Diabetes	+
6.	Diabetes	Pre-diabetes	+
7.	Pre-diabetes	Pre-diabetes	+
8.	Diabetes	Diabetes	+
9.	Diabetes	Diabetes	+
10.	Pre-diabetes	Diabetes	+
11.	Pre-diabetes	Pre-diabetes	+
12.	Diabetes	Diabetes	+
13.	Pre-diabetes	Diabetes	+
14.	Diabetes	Diabetes	+
15.	Pre-diabetes	Pre-diabetes	+
16.	Pre-diabetes	Diabetes	+
17.	Diabetes	Diabetes	+
18.	Diabetes	Diabetes	+
19.	Diabetes	Diabetes	+
20.	Diabetes	Diabetes	+
21.	Diabetes	Diabetes	+
22.	Pre-diabetes	Pre-diabetes	+
23.	Pre-diabetes	Pre-diabetes	+
24.	Pre-diabetes	Normal	+
25.	Pre-diabetes	Pre-diabetes	+
26.	Diabetes	Diabetes	+
27.	Pre-diabetes	Pre-diabetes	+

Note:
+: The patient experienced a new-onset type 2 DM
-: The patient did not experience a new-onset type 2 DM

Patient distribution based on gender

Patients who took simvastatin in this study were predominantly male than female. It means that cardiovascular disease is more common in men, and this result is supported by the study of the Australian Institute of Health and Welfare (2020) that men have the probability of experiencing coronary heart disease (CHD) at least twice higher compared to women [21]. Weidner (2010) has shown that men are exposed to increased coronary heart disease due to excessive drinking and smoking habits. Additionally, stressed men are physiologically, behaviorally, and emotionally less adaptive, which contribute to an increased risk of coronary heart disease [22].

The estrogen hormone, ethinylestradiol produced in women, has an atheroprotective effect that lowers LDL, increases HDL, possesses antioxidant activity, and has a direct biological impact on cardiovascular tissues [23]. This hormone protects women from cardiovascular disease before menopause. After menopause, the cardiovascular disease risk in women is almost as high as men. Atherosclerosis is an active process that involves pro-inflammatory mediators. The inflammatory immune system plays a major role in the development of fatty streaks. Besides, the hormone estrogen helps prevent the development of fatty streaks [24]. Gender will influence atherosclerotic plaque formation, susceptibility, and clinical manifestations. Similarly, Lansky *et al.* (2012) stated that men have a greater atherosclerosis risk because the development of atherosclerotic lesions in women takes seven to eight years longer. Men with acute coronary syndrome (ACS) are more prone to rupture, while women only experience plaque erosion. Therefore, it is easier for men to develop a more severe cardiovascular disease compared to women. This is possible since estrogen functions to slow the development of plaque, stabilize existing ones, and prevent rupture in women [25].

Patient distribution based on age

The age used as an inclusion criterion in this study was ≥50 years because degenerative diseases are common in the elderly [25, 26]. The function of the human organs decreases as age increases. It is evident in the activities of LDL receptors, which consistently decrease in older adults. Aging causes the fat spots in the body to increase and the total cholesterol levels to be very high. Meanwhile, HDL levels remained relatively unchanged. Changes in cholesterol profile can also be influenced by other factors, such as lifestyle, family history, and diet [4].

Simvastatin dosage

The simvastatin dose used in the inclusion criteria might be 10 mg or 20 mg per day in this study. However, the physicians

prescribed simvastatin at a dose of 20 mg/day for all patients. According to ACC/AHA (2018) and PERKENI[a] (2019), the daily dose of simvastatin, which has a moderate intensity effect or can lower LDL levels by 30% to less than 50%, is 20 mg/day [1, 11]. Meanwhile, for low-intensity effects or only to reduce the LDL level lower than 30%, simvastatin can be given with a smaller daily dose of 10 mg/day. However, simvastatin does not have a high-intensity effect because it cannot reduce the LDL level equal to or higher than 50%. Atorvastatin 40-80 mg and rosuvastatin 20-40 mg are statin therapy with high-intensity effects [11]. Simvastatin 20 mg/day with moderate intensity effects may provide better benefits to ischemic stroke patients than high-intensity statins, including lower risk of major adverse cardiac events, lower recurrent ischemic and hemorrhagic stroke, as well as a lower risk of experiencing recurrent hospitalizations for cardiovascular disease [13, 27, 28].

New-onset type 2 DM due to long-term use of simvastatin

This study aims to determine the risk of a relatively new side effect associated with prolonged use of simvastatin, such as the new-onset type 2 DM. The parameters observed were an increase in the FPG levels and serum HbA1C. Furthermore, observations were made twice in the first and third months since the enrolment of the patients. The examination of the two parameters showed that all patients have side effects, which is the type 2 diabetes mellitus. This should be monitored and followed up to prevent further health problems in patients who have not experienced increased blood glucose profiles and diabetes. This result was consistent with a meta-analysis study conducted by Kamran *et al.* (2018) regarding the new-onset DM in patients using statin therapy [29]. As a result, the FDA has issued a warning that statins can affect glycemic control because of increased FPG and serum HbA1C levels [15]. Similarly, Roy *et al.* (2019) reported the new-onset diabetes incidence in dyslipidemic patients using statins with a prevalence of 7.03%. Thus, the main risk factors that induce new-onset diabetes are patients over 60 years of age, treatment using rosuvastatin, and a long duration and high dose of Statin [30].

The FPG and HbA1C levels were the two parameters used to determine the side effects of the new-onset type 2 DM, either an increase in just one or both. According to PERKENI[b] or the Indonesian Society of Endocrinology (2019) and American Diabetes Association (2020), the criteria for examining these two parameters are classified as normal, pre-diabetes, or diabetes [19, 20].

Hemoglobin A1c (HbA1c) can be used as a biomarker for monitoring glucose levels in patients with diabetes. About 6% of HbA is HbA1, consisting of HbA1a1, HbA1a2, HbA1b, and HbA1ac. HbA1c has the most significant fraction, about 5% of the total HbA1. Glycated hemoglobin (HbA1c) is a compound formed from the chemical reaction between glucose and hemoglobin through a non-enzymatic reaction between glucose and the N-terminal valine in the beta chain of hemoglobin A. Glucose forms aldimine bonds with NH2- from valine in the beta chain. HbA1c in the body will be stored in erythrocytes and degrades slowly throughout the erythrocytes lifespan of 3 to 4 months. The glycated hemoglobin level depends on the blood glucose availability, and the glucose attached to hemoglobin is very stable. Thus, globally, HbA1c has become one of the tests for diabetes [31]. HbA1c is a protein formed from the glucose and hemoglobin combination in red blood cells. The examination of HbA1c levels is conducted to determine the blood glucose balance. However, the value was not influenced by fluctuations in daily blood glucose levels and short-term lifestyles. This examination describes the control of blood glucose metabolism during the previous three to four months. It is also a valuable indicator to monitor the extent to which blood glucose levels are controlled and to investigate the effects of diet and exercise on blood glucose levels [32].

This study showed a discrepancy between FPG and serum HbA1c levels. There were 18 patients (66.67%) with normal FPG levels but had abnormal serum HbA1c levels. When the FPG level is normal, the serum HbA1c level should be normal. It is influenced by lifestyle factors, such as the patient's control on diet and exercise before examining blood glucose profile levels (FPG and HbA1c). However, the patient did not make lifestyle improvements in the following days, which caused the blood glucose profile measured did not to describe the actual situation. Statins can induce insulin resistance due to the inhibition of isoprenoids biosynthesis. Similarly, decreased synthesis of isoprenoids may cause down-regulation of GLUT-4 (glucose transporter protein) in adipocyte cells. This leads to reduced absorption of insulin-glucose uptake and glucose intolerance [33].

Furthermore, it causes DM by affecting glucose homeostasis. It is achieved when there is an interference with insulin secretion and sensitivity. Also, when cholesterol synthesis occurs through acetyl-CoA, several metabolites, such as isoprenoids and CoQ10, are produced. However, when statins are consumed, there can be a decrease in CoQ10, which may cause a gradual reduction in insulin levels. The CoQ10 biosynthesis inhibition can lead to a down-regulation of GLUT-4 in adipocyte tissue and mediate insulin uptake stimulation from glucose in skeletal muscle and adipose tissue [34].

The decrease in insulin due to prolonged use of statins can also be influenced by other factors, such as food consumption. Excessive consumption will cause imbalanced energy in the body, especially from foods containing carbohydrates and fats. Excessive consumption of an unbalanced diet may lead to obesity, which is a risk factor for DM disease [35]. Besides, the lack of physical activity is also a significant risk factor that contributes to DM. Lack of physical activity and abdominal obesity are the risk factors of cardiometabolic disorders. Physical activity is an effective way to control blood glucose levels in type 2 DM patients. The body uses glucose as fuel to produce energy for physical activities. Glucose is the body that comes from the blood, liver, and muscles. Glucose is the form of glycogen is stored in the liver and muscles. During the first 15 minutes of physical exercise, most fuel comes from glucose in the bloodstream or glycogen in muscles. However, after exercising

for 30 minutes, the body begins to use glucose from the blood, liver, and muscles to obtain more energy, decreasing blood glucose and glycogen levels [36].

Conclusion

From the results of this study, 27 patients who routinely consumed 20 mg of simvastatin with a minimum usage duration of 6 months experienced a new-onset type 2 DM. However, this condition is new in Indonesia and is still not a concern. Therefore, a routine examination of the blood glucose profile is critical and recommended for patients who intend to use 20 mg of simvastatin for a long time.

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Conflict of interest: None

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Ethics statement: This research protocol has followed the guidelines in the Declaration of Helsinki. The Ethical Approval Letter (No.450/EC/KEPK/12/2017) was issued by the Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya.

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