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Evaluation of Statin Therapy on Lipid Profile of Diabetic Dyslipidemia Patients

Soebagijo Adi Soelistijo[1*], Wynne Widiarti[2], Bambang Hermanto[3]

[1]Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
[2]Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia
[3]Department of Pharmacology and Therapeutics, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

ABSTRACT

The incidence of diabetes mellitus in Indonesia continues to increase. Diabetic dyslipidemia, as one of the complications, significantly increase the risk of developing cardiovascular disease causing 65% of death in diabetes patients. This study evaluated the statin therapy and comorbidity factors on lipid profile of diabetic dyslipidemia patients. A cross-sectional study consisted of patients who received and did not received statin therapy. The achievement of LDL cholesterol target was determined according to the ATP III guidelines. Related comorbidity factors were also evaluated. There were 36 patients (12%) who received statin therapy and 86 patients (28.7%) who did not receive statin therapy, achieving the LDL cholesterol target. The achievement of LDL cholesterol target was associated with the presence of statin therapy (p = 0.000). Stroke, hypertension, and peripheral arterial disease (PAD) as the comorbidity factors were not associated with these variables, while coronary heart disease (CHD) was associated with the presence of statin therapy (p = 0.008), the achievement of LDL cholesterol target (p = 0.007), and the duration of statin therapy (p = 0.022). The achievement of LDL cholesterol target was associated with the presence of statin therapy. CHD as the comorbidity factors was associated with the presence of statin therapy, the achievement of LDL cholesterol target, and the duration of statin therapy.

Keywords: diabetic dyslipidemia, lipid profile, statin

Correspondence:
Soebagijo Adi Soelistijo, MD
Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
Prof. Dr. Moestopo Street 4-6, Surabaya
Tel: +6231-502-3865; Fax: +6231-502-3865
E-mail: soebagijo@yahoo.com

INTRODUCTION

The incidence of diabetes mellitus in Indonesia continues to increase due to unhealthy lifestyle of Indonesian. According to International Diabetes Federation (IDF) 2017, the number of diabetes mellitus patients in Indonesia is ranked 6th highest in the world, estimated to reach 10.3 million people. From these data, there are still 73.7% Indonesians with diabetes symptoms but remaining undiagnosed. IDF estimates that diabetes mellitus patients in Indonesia will reach 16.7 million people in 2045 (1). In addition, some studies report that patients with diabetes mellitus are diagnosed with metabolic syndrome (2,3).

Diabetes mellitus is a metabolic syndrome due to impaired insulin action (4). Symptoms of diabetes mellitus includes hyperglycemia, polyuria, polydipsia, weight loss, and sometimes accompanied with polyphagia and vision disturbance [1]. Diabetes mellitus itself can develop into several complications because chronic hyperglycemia state damages various organ functions, such as retinopathy, neuropathy, and gangrene (5,6). Diabetes mellitus can also develop into diabetic dyslipidemia significantly increasing the risk of cardiovascular disease (7). At the same time, 9.9% of death in diabetes mellitus patients are caused by cardiovascular disease (8).

High cholesterol is associated with diabetes mellitus (9). Diabetic dyslipidemia is characterized with elevated low-density lipoprotein (LDL) and triglycerides (TG) and decreased high-density lipoprotein (HDL) [2]. Diabetic dyslipidemia is more dangerous with high and uncontrolled blood sugar levels (10). Diabetic dyslipidemia facilitates the process of atherosclerosis and will eventually lead to coronary heart disease (CHD). When the plaque thickens and clogs blood vessels, stroke may also occur (11). Hence, diabetic dyslipidemia patients must control their lipid profile to prevent the occurrence of cardiovascular disease. The lipid profile improvement of diabetic dyslipidemia focuses on the LDL cholesterol level that plays major role in the development of atherosclerosis [3]. The atherosclerosis risk factors explain just of a minor part of the excess incidence of vascular disease among diabetes mellitus (12). Treatments that can be done for diabetic dyslipidemia are lifestyle modification and pharmacological therapy, in the form of statins, chosen as the first line lipid lowering agent for diabetic dyslipidemia (13). In addition, blood glucose level control is also important. If patients have good self-care behavior and self-management education, diabetes will be controlled to avoid complications and make patients have a better quality of life (14,15).

Therefore, this study aimed to evaluate the efficacy of statin therapy in controlling the lipid profile of diabetic dyslipidemia patients [4]. This study compared the lipid profile of diabetic dyslipidemia patients who received statin therapy to those who did not. This study also observed the comorbidity factors that may affect the LDL cholesterol level, including stroke, hypertension, CHD, and peripheral arterial disease (PAD).

METHODS

This retrospective cross-sectional study used secondary data from medical records in Dr. Soetomo General Hospital, Surabaya, Indonesia. We specifically used all outpatients from internal medicine clinic of Dr. Soetomo General Hospital, Surabaya, from January to December 2018. This study included all patients with diagnosis of diabetes mellitus,

based on ICD 10. Then, patients that received lipid lowering drugs other than statins were excluded because we only wanted to evaluate statin therapy effect on its own. Patients that received statin therapy less than 3 months were also excluded from this study because American Diabetes Association (ADA) standards of medical care (2018) recommend to evaluate statin therapy 4-12 weeks after initiation therapy. Hence, we decided to evaluate the statin therapy effect after 12 weeks (16). Last, we also excluded incomplete medical records. Our samples were divided into two groups: patients who did not receive statin therapy and patients who received statin therapy. Thus, this study took 300 samples from each group. In total, there were 600 samples from both groups.

From the medical records, we gathered several data, including initial and final lipid profile, type of statins, statins dosage, duration of statin therapy, and comorbidity factors, including stroke, hypertension, CHD, and PAD. The subjectivity in writing the medical records would not affect our data because the data collection did not involve any physical examination or opinions from the attending physician. Thus, the data used in this study were all reliable. For validity, this study excluded incomplete medical records.

We sorted out the sample based on ICD 10 diagnosis code. We included patients diagnosed with cerebral infarction and stroke to the group that had stroke as their comorbidity factor. At the same time, for hypertension as the comorbidity factor, we included all patients diagnosed with every hypertensive disease. Then, for CHD as the comorbidity factor, we included patients with diagnosis of myocardial infarction, ischemic cardiomyopathy, and coronary heart disease. We also included patients diagnosed with peripheral vascular disease to the group that had PAD as their comorbidity factor.

Statistical Analysis

Bivariate analysis was used to determine the association between each variable. This study analyzed the data with comparing both sample groups using spearman correlation test. We analyzed the association between the presences of statin therapy with the achievement of LDL cholesterol target based on ATP III guideline (2001). We also analyzed the association between the duration of statin therapy with the achievement of LDL cholesterol target. Moreover, to evaluate the related comorbidity factors, we analyzed the association between each comorbidity factor with the presence of statin therapy, the achievement of LDL cholesterol target and the duration of statin therapy. We analyzed the data with SPSS software Version 26 and set the statistical significance level at 0.05.

RESULTS

After gathering 600 samples, we summarize the patients' characteristics in Table 1. We found that all diabetic dyslipidemia patients, included in this study, received moderate intensity statin therapy (n=300; 100.0%). The duration of statin therapy from both groups was categorized into three groups: 3-6 months, 7-12 months, and >12 months. Most patients received statin therapy for 3-6 months (n=110; 36.7%), while 97 patients received statin therapy for 7-12 months, and the rest received statin therapy for more than 12 months (n=93; 31.0%). Most patients included in this study had hypertension as their comorbidity factor in both group (n=209; 34.8%). Meanwhile, the fewest comorbidity factor from both groups was PAD (n=8; 1.3%).

Table 1. Patients' baseline characteristics

Characteristics	With Statin Therapy	Without Statin Therapy
Age (years)	58.03±8.4	56.09±9.9
Sex		
Male	115 (38.3%)	139 (46.3%)
Female	185 (61.7%)	161 (53.7%)
Initial LDL Cholesterol Level (mg/dL)	144.7±34.4	126.3± 43.8
Final LDL Cholesterol Level (mg/dL)	131.6±35.4	123.7±41.1
Initial HDL Cholesterol Level (mg/dL)	48.57±12.6	41.68±13.1
Final HDL Cholesterol Level (mg/dL)	53.17±20.8	46.67±18.0
Initial TG Cholesterol Level (mg/dL)	166.18±86.4	163.10±101.7
Final TG Cholesterol Level (mg/dL)	160.44±113.6	146.99±94.2
LDL Cholesterol Level on Target	36 (12.0%)	86 (28.7%)
LDL Cholesterol Level Not on Target	264 (88.0%)	214 (71.3%)
Type of statin therapy		
Moderate Intensity	300 (100.0%)	-
High Intensity	0	-
Duration of statin therapy		
3-6 months	110 (36.7%)	-
7-12 months	97 (32.3%)	-
> 12 months	93 (31.0%)	-
Comorbidity Factors		
Stroke	18 (6.0%)	26 (8.7%)
Hypertension	111 (37.0%)	98 (32.7%)
CHD	50 (16.7%)	28 (9.3%)
PAD	6 (2.0%)	2 (0.7%)

LDL: low-density lipoprotein; TG: triglycerides; HDL: high-density lipoprotein; CHD: coronary heart disease; PAD: peripheral arterial disease
Data are presented as Mean±SD and Number of Patients (Percentage %)

The association between the presences and the duration of statin therapy with the achievement of LDL cholesterol target based on ATP III guideline (2001)

This study found that most patients in both groups did not achieve LDL cholesterol target according to the ATP III guideline as shown in Table 2. There were 264 patients (88.0%) that did not reach the LDL cholesterol target after getting statin therapy. The rest 36 patients (12.0%) who received statin therapy reached the LDL cholesterol target. For the group that did not receive statin therapy, 214 patients (71.3%) also did not reach their LDL cholesterol target. The presence of statin therapy associated with achievement of LDL cholesterol target ($p = 0.000$), while the duration of statin therapy was not associated with achievement of LDL cholesterol target ($p = 0.836$).

Table 2. The achievement of LDL cholesterol target from both groups

Variables	LDL Cholesterol Level Achievement		p	Coefficient correlation
	Not on Target	On Target		

Statin Therapy			0.000*	-0.207
Yes	264 (88.0%)	36 (12.0%)		
No	214 (71.3%)	86 (28.7%)		
Duration of statin therapy			0.836	-0.012
3-6 months	196 (32.7%)	51 (8.5%)		
7-12 months	163 (27.2%)	44 (7.3%)		
>12 months	119 (19.8%)	27 (4.5%)		
LDL: low-density lipoprotein *p <0.05 (significantly correlated)				

The association between each comorbidity factor with the presence of statin therapy, the achievement of LDL cholesterol target, and the duration of statin therapy.

Table 3 shows the comorbidity factor with the presence of statin therapy. From four comorbidity factors, the achievement of LDL cholesterol target was inversely associated with CHD as the comorbidity factor (p = 0.008; correlation coefficient = 0.109).

Table 3. The comorbidity factor with the presence of statin therapy

Comorbidity Factors	Statin therapy		p	Correlation Coefficient
	Yes	No		
Stroke			0.211	-0.511
Yes	18 (3.0%)	26 (4.3%)		
No	274 (45.7%)	282 (46.0%)		
Hypertension			0.266	0.045
Yes	111 (18.5%)	189 (31.5%)		
No	98 (16.3%)	202 (33.7%)		
CHD			0.008*	0.109
Yes	50 (8.3%)	28 (4.7%)		
No	250 (41.7%)	272 (45.3%)		
PAD			0.155	0.058
Yes	6 (1.0%)	2 (0.3%)		
No	294 (49.0%)	298 (49.7%)		
CHD: coronary heart disease; PAD: peripheral arterial disease *p <0.05 (significantly correlated)				

Table 4 shows the comorbidity factor with the achievement of LDL cholesterol target. From four comorbidity factors, only the CHD was inversely associated with achievement of LDL cholesterol target (p = 0.007; correlation coefficient = -0.109).

Table 4. The comorbidity factor with the achievement of LDL cholesterol target

Comorbidity Factors	LDL Cholesterol Level Achievement		p	Correlation Coefficient
	Not on Target	On Target		
Stroke			0.236	0.049
Yes	32 (5.3%)	12 (2.0%)		
No	446 (74.3%)	110 (18.3%)		
Hypertension			0.749	0.013
Yes	165 (27.5%)	44 (7.3%)		
No	313 (52.2%)	78 (13.0%)		
CHD			0.007*	-0.109
Yes	71 (11.8%)	7 (1.2%)		
No	407 (67.8%)	115 (19.2%)		
PAD			0.151	-0.059
Yes	8 (1.3%)	0		
No	470 (78.3%)	122 (20.3%)		
LDL: low-density lipoprotein; CHD: coronary heart disease; PAD: peripheral arterial disease *p <0.05 (significantly correlated)				

Table 5 shows the comorbidity factor with the achievement of LDL cholesterol target. From four comorbidity factors, only the CHD was inversely associated the duration of statin therapy (p = 0.022; correlation coefficient = -0.133).

Table 5. The comorbidity factor with the duration of statin therapy

Comorbidity Factors	Duration of statin therapy			p	Correlation Coefficient
	3-6 months	7-12 months	>12 months		
Stroke				0.551	0.035
Yes	20 (3.3%)	15 (2.5%)	9 (1.5%)		
No	227 (37.8%)	192 (32.0%)	137 (22.8%)		
Hypertension				0.074	0.103
Yes	77 (12.8%)	82 (13.7%)	50 (8.3%)		
No	170 (28.3%)	125 (20.8%)	96 (16.0%)		
CHD				0.022*	-0.133
Yes	34 (5.7%)	32 (5.3%)	12 (2.0%)		
No	213 (35.5%)	175 (29.2%)	134 (22.3%)		
PAD				0.406	-0.048
Yes	3 (0.5%)	5 (0.8%)	0		
No	244 (40.7%)	202 (33.7%)	146 (24.3%)		
CHD: coronary heart disease; PAD: peripheral arterial disease *p <0.05 (significantly correlated)					

DISCUSSION

Although most diabetic dyslipidemia patients did not achieve their LDL cholesterol target, the achievement of LDL cholesterol target was significantly associated with the presence of statin therapy. Statin therapy is chosen as the most effective therapy for both non-diabetic and diabetic patients (17). Another report also proved through the research that the result of statin therapy on diabetes patients who had cardiovascular disease was consistently superior compared to ordinary patients, measured based on the LDL cholesterol level (18).

Generally, the LDL cholesterol level of diabetic dyslipidemia patients does not differ enormously with the population of non-diabetic patients (19). However, in diabetic dyslipidemia patients, there is an increase of sdLDL level that tends to be more atherogenic and increase the risk of the development of cardiovascular disease (20). Moreover, after reviewing statin therapy for 5 years, the MRC/BHF study in 2003 stated that 40 mg of simvastatin therapy could decrease the LDL

cholesterol level up to 39 mg/dL (1.0 mmol/L). This reduction is considered to reduce the risk of the development of CHD and stroke (21). In addition, the moderate intensity statin therapy is found to decrease the LDL cholesterol level up to 40%. The therapy of 10 mg atorvastatin can decrease the LDL cholesterol level up to 46.8 mg/dL (1,2 mmol/L) (22). Previous report found that higher dose of atorvastatin caused more significant decrease in LDL cholesterol level (23). It is similar to another study stating that rosuvastatin 10 mg and atorvastatin 10 mg had more significant effect than simvastatin 10 mg within 12 weeks of therapy (24).

Moreover, diabetic patients tend to have lower HDL cholesterol level and higher triglyceride cholesterol level. These conditions can be improved by good blood glucose control (25). From the lipid profile, this study found that average final HDL cholesterol level in both groups were classified into borderline risk group (40-59 mg/dL). In addition, group that did not receive statin therapy experienced more reduction in HDL cholesterol level. For the triglyceride cholesterol level, the data revealed that initial and final triglyceride level of both groups were categorized as borderline risk group (150-399 mg/dL) (26). On the other hand, group that did not receive statin therapy experienced more significant decrease in triglyceride cholesterol level.

According to previous report, only 44% of diabetic dyslipidemia patients could achieve their LDL cholesterol target after getting moderate intensity statin (27). Similar result to another study found that only 37.6% of diabetes patients could achieve the LDL cholesterol target, based on NCEP ATP III guideline (LDL <100 mg/dL) (28). In this study, there were 12.0% of patients who achieved the LDL cholesterol level target after getting statin therapy. On the other hand, in the group that did not receive statin therapy, there were 86 patients (28.7%) who achieved the LDL cholesterol level target. The achievement of LDL cholesterol target was determined according to the ATP III guideline (2001). This result is identical to other studies, although patients who achieved the LDL cholesterol target in this study were much lower. This result was certainly influenced by various factors, including the patient's adherence in taking the drug (which was not examined in this study), difference in the duration, and type and dosage of statin therapy that was prescribed to the patient. This study also found that there was no patient that received high intensity statin therapy. Therefore, this study could not reveal the superiority of high intensity statin therapy, that proven by other study (29).

Based on the Heart Protection Study Collaborative Group (2011), long term use of statins does not show any harmful side effects. Even for the effect of reducing the mortality of diabetic dyslipidemia patients, it remains consistent in protecting the patient for up to 11 years of therapy (21). Also, statin therapy in diabetic dyslipidemia patients does not affect blood glucose control (29). In addition, the safety of statin therapy in Asian race has narrower therapeutic dose interval (30).

MRC/BHF Heart Protection Study (2003) found that the allocation of simvastatin 40 mg for diabetes patients was significantly useful for preventing cardiovascular disease, both for patients who never had of cardiovascular disease and patients who had been. This condition was proven with the reduction of CHD cases in those patients after 5 years of therapy (31). Also, previous study found that 37.0% of diabetic dyslipidemia patients achieved the LDL cholesterol level target within 12 weeks, and 54.1% diabetic dyslipidemia patients achieved the LDL cholesterol level target within 24 weeks, with 10 mg of atorvastatin therapy. For the HDL cholesterol level, it began to increase significantly after 24 weeks of atorvastatin 10 mg therapy (32). However, this study found that the achievement of LDL cholesterol target was not associated with the duration of statin therapy. This result was certainly affected by the relatively short duration of observation, compared to other studies. In addition, this study did not find any diabetic dyslipidemia patients who received high intensity statin therapy.

Some journals stated that the achievement of LDL cholesterol target of diabetic dyslipidemia patients was associated with CHD as the comorbidity factor. A study found that diabetic dyslipidemia patients who had CHD achieved their LDL cholesterol target better than ordinary patients (18). Similar results were also obtained by the ALLHAT Collaborative Research Group in 2002, which used 40 mg of pravastatin (33). In the another study, it was found that the hospital admissions rate related to cardiovascular disease was decreased by 55% in diabetic dyslipidemia patients who received statin therapy (34).

In this study, it was found that CHD, as the comorbidity factor, was associated with the presence of statin therapy, the achievement of LDL cholesterol target, and the duration of statin therapy. CHD was inversely associated with the presence of statin therapy and the duration of statin therapy. From this result, it can be concluded that patients who did not receive statin therapy did not have solid indication of statin therapy. Thus, group that did not receive statin therapy had more optimal final LDL cholesterol level. The duration of statin therapy was also inversely associated with CHD, as the comorbidity factor, in line with the results of other studies (21).

Generally, statin therapy significantly reduces the risk of developing CHD in diabetic dyslipidemia patients (35). Other studies also found that different type of statins caused significant decreased in number of CHD cases (36). The number of CHD cases in patients who received 80 mg of atorvastatin (high intensity statin) was 16% lower than patients who received 40 mg of pravastatin (moderate intensity statin). Then, that study also found that the group of patients who received 80 mg of atorvastatin had lower number of the additional CHD cases by 19% (36). However, our study found that CHD, as the comorbidity factor, was more prevalent in the group that received statin therapy. This condition is contrary to other studies result stating that statin therapy reduced the prevalence of CHD attack (37-40).

We acknowledged that the lack of information in the medical records made several aspects could not be examined in this study. Moreover, this study also used secondary data. It can be seen that there were diversified type, dosage, and duration of statin therapy in each patient. In addition, the variables of this study were very limited. There were still many aspects that had not been discussed in this study. One of those aspects is patients' adherence in taking their medication.

CONCLUSION

The achievement of LDL cholesterol target in diabetic dyslipidemias patients determined according to the ATP III guideline was associated with the presence of therapy. The achievement of LDL cholesterol target was not associated with the duration of statin therapy. For the comorbidity factors, stroke, hypertension, and PAD were not associated with the achievement of LDL cholesterol target, the presence of statin therapy, and the duration of statin therapy. However, CHD, as the comorbidity factor, was proven to be associated

with the achievement of LDL cholesterol target, the presence of statin therapy, and the duration of statin therapy.

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