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Comparison of Atorvastatin and Simvastatin Modulation on Adiponectin and Insulin Resistance In Non-Diabetic Dyslipidemic Patients

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ABSTRACT

Statins are the first-line treatment of dyslipidemia but their use is associated with an increased risk of impaired glycemic control. In this study, the effects of atorvastatin and simvastatin on adiponectin levels and insulin resistance index were compared in non-diabetic dyslipidemic patients. Thirty-nine dyslipidemic non-diabetic outpatients were included in this study. The patients were prescribed with either simvastatin 20 mg or atorvastatin 20 mg. Blood sampling was carried out before and two months after statin treatments to measure the adiponectin, insulin, and fasting blood glucose (FBG) levels. The insulin resistance index was calculated based on the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR). Most patients had low baseline adiponectin levels (<3 μg/dl) and were not significantly changed after two months of atorvastatin or simvastatin treatment. The fasting insulin levels significantly increased in the simvastatin group (p=0.033), but not in the atorvastatin group. The HOMA-IR index was also increased in the simvastatin group from 1.89 ± 4.51 before to 2.72 ± 5.86 after treatment but did not reach statistical significance. Further analysis found a positive correlation between fasting insulin level and HOMA-IR value and the simvastatin group's adiponectin level (p=0.001). There is an indication that simvastatin, but not atorvastatin, stimulates an increase in fasting insulin levels after two months of treatments. The increase in the insulin resistance index correlates to the plasma level of adiponectin. Further study with a longer duration of observation is required to address this potential side effect.

Keywords: Simvastatin; atorvastatin; glycemic control; adiponectin; insulin resistance index

Introduction

Dyslipidemia is a metabolism disorder characterized by increased total cholesterol and low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) levels (1). Dyslipidemia can be triggered by high-fat diet leading to metabolic disorders, both in humans (2) and animal models (3). Statins have been established as the first-line therapy for dyslipidemia, since they can reduce LDL-C levels and decrease the risks of coronary heart diseases, stroke, and death (4). Statins act by inhibiting the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase which is responsible for cholesterol biosynthesis (5). The inhibition of HMG-CoA reductase activity may also generate a pleiotropic effect (6), adding further benefits for statin use in hypercholesterolemic patients (7).

Since 2012, the Food and Drug Administration (FDA) has disclosed the risk of hyperglycemia and increased glycosylated hemoglobin (HbA_{1C}) by statins. Based on observational studies and meta-analysis, around 10-12% of the new onset of diabetes mellitus (NODM) has been implicated with the use of statins (8). This leads to controversy on statin use in patients with diabetes mellitus (9). Several hypotheses try to explain the mechanism of statin-induced diabetogenesis, including the impairment of pancreatic beta-cell function and reduction of insulin sensitivity by statins (8). However, whether the

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diabetogenic risks of statins are similar to all types of statins remains disputed (8).

Insulin is a polypeptide that is synthesized and released from the β-cell pancreas, thus, the level of insulin is depleted during pancreatic damage (10). However, the diabetogenic effect of statins is not likely to be related to pancreatic injury. Instead, plasma adiponectin level, a specific protein in adipose tissue, has been claimed as a good indicator of insulin sensitivity as reduced adiponectin levels may lead to impaired glucose metabolism (11). Clinical studies have shown a decrease in plasma adiponectin is mostly found in obese individuals, type-2 diabetes mellitus, metabolic syndrome, and coronary artery disease patients (12). Adiponectin has been demonstrated to stimulate insulin gene expression in pancreatic β-cells (13). In addition, the anti-apoptotic effect of adiponectin may protect against pancreatic β-cell apoptosis, thereby, increasing insulin production (14).

Several reports have shown that statin-induced insulin resistance is associated with reduced plasma adiponectin levels (15, 16). However, the effects of statin therapy on adiponectin levels remain contradictory as some studies also demonstrate no change or increased adiponectin levels in patients receiving different types of statins (17-19). Therefore, this study aimed to compare the effect of atorvastatin and simvastatin use on adiponectin levels and insulin resistance index in patients diagnosed with nondiabetic dyslipidemia.

Material and Methods

Subjects: The subjects were recruited from consecutive outpatients (n=39) attending Universitas Hasanuddin teaching hospitals and Labuang Baji regional hospitals in Makassar, Indonesia. The diagnosis of dyslipidemia is defined if the patients meet one of the categories of dyslipidemia according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), i.e increased plasma levels of total cholesterol ≥200 mg/dL, low-density lipoprotein (LDL) cholesterol ≥100 mg/dL, triglycerides ≥150 mg/dL, and reduced high-density lipoprotein (HDL) cholesterol <40 mg/dL. Patients with type-2 diabetes mellitus (T2DM) were excluded from this study. All subjects were adults (>18 years old) and prescribed with either simvastatin 20 mg/day or atorvastatin 20 mg/day. Subjects who met the inclusion criteria have been explained about the study and have signed the informed consent before participating in this study.

Data Collection: All procedures carried out in this study complied with the institutional policy and protocols for human subject research studies and have been granted an ethical clearance (No. 832/UN4.6.4.5.31/PP36/2019). Questionnaires, medical records, and direct interviews were used to obtain patients' details, history of treatments and diseases, diets, and physical activities. Physical activities were categorized (as low, moderate, or high) based on the international physical activities questionnaire (IPAQ) (20). The measurement of body mass index (BMI) is performed by anthropometric techniques.

Patients were divided into two treatment groups, either simvastatin or atorvastatin group. Blood samples were withdrawn prior to initiation and following 2 months post statin therapy. The lipid profiles and fasting blood glucose (FBG) levels were measured using a hematology analyzer (ABX Pentra 60, HORIBA). Meanwhile, the plasma levels of adiponectin and insulin were measured using an enzyme-like immunosorbent assay (ELISA) reader (Thermo Fisher Scientific) with human adiponectin or insulin ELISA kit (Bioassay Technology Laboratory). Based on the FBG and fasting insulin levels, the insulin resistance index was calculated using the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) calculations (21):

$$\text{HOMA-IR} = \frac{\text{Fasting insulin (}\mu\text{U/mL)} \times \text{FBG (mmol/L)}}{22.5}$$

Statistical Analysis: Data are presented as mean ± standard deviation. The distribution of data was analyzed using a Kolmogorov-Smirnov analysis. Since data were not normally distributed, the significant difference between the two groups was compared using a Mann-Whitney U-test, while the differences between pre- and post-treatments were analyzed with a Wilcoxon test. The correlation analysis was performed using Spearman's rho correlation analysis. A significant difference or correlation is defined if the p-value is less than 0.05.

Results

The demographic data collected include sex, age, body mass index (BMI), physical activities, and medication history. The details of patients' demography are presented in Table 1.

Table 1: The Demographic Data of Non-Diabetic Dyslipidemic Patients Receiving Either 20 mg Atorvastatin or 20 mg Simvastatin

Patients' demography	Atorvastatin (N, %)	Simvastatin (N, %)	P value
Sex			
Male	9 (45)	11 (58)	0.427
Female	11 (55)	8 (42)	
Age (years)			
35-45	1 (5)	0 (0)	
46-55	7 (35)	4 (21)	0.028
56-65	8 (40)	4 (21)	
>66	4 (20)	11 (58)	
BMI (kg/m^2)			
>25 (obese)	10 (50)	9 (47)	
23-24.9 (overweight)	6 (30)	6 (32)	0.927
18.5-22.9 (normal)	3 (15)	4 (21)	
<18.5 (underweight)	1 (5)	0 (0)	
Physical activity[a]			
Low	8 (40)	8 (42)	0.895
Moderate	12 (60)	11 (58)	
High	0 (0)	0 (0)	
Medication history[b]			
ACEI	3 (15)	6 (32)	
ARB	8 (40)	9 (47)	0.238
BB	12 (60)	14 (74)	
CCB	6 (30)	7 (37)	

[a]Based on the IPAQ 2005 questionnaires. BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blocker; CCB: calcium channel inhibitor. [b]Most patients received a combination of antihypertensive agents

Table 2: The Mean Adiponectin, Fasting Blood Glucose, Fasting Insulin Levels, and HOMA-IR Value in The Atorvastatin and Simvastatin Groups

Treatment	Variables	Baseline	Post-treatment	p-value
Atorvastatin	Adiponectin (mg/L)	8.44 ± 17.33	5.72 ± 9.18	0.841
	Fasting insulin (μU/mL)	6.93 ± 14.02	7.07 ±15.02	0.794
	FBG (mg/dl)	105.3 ± 13.44	109.7 ± 31.97	0.968
	HOMA-IR	1.82 ± 3.77	1.89 ± 4.11	0.940
Simvastatin	Adiponectin (mg/L)	7.66 ± 14.06	11.05 ± 23.27	0.260
	Fasting insulin (μU/mL)	7.28 ± 16.68	11.83 ± 26.74	0.033*
	FBG (mg/dl)	101.0 ± 13.18	100.2 ± 10.88	0.798
	HOMA-IR	1.89 ± 4.51	2.72 ± 5.86	0.107

Data expressed as mean ± SD; FBG: Fasting Blood Glucose; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance; p-values based on Wilcoxon test

This study involved 39 non-diabetic dyslipidemic patients, consisting of 20 male (51%) and 19 female patients (49%). The majority of these dyslipidemic patients aged between 46 and 65 years old (59%). Many of them were overweight (31%) or obese (49%). Based on the questionnaires, it was found that more subjects performed moderate-intensity physical activities (59%) but none engaged in high-intensity exercise. All of the subjects were treated with

Table 3: The Number of Subjects with Low, Normal, or High Levels of Adiponectin, Fasting Insulin, and HOMA-IR in the Atorvastatin and Simvastatin Groups

Variables	Categories	Atorvastatin (n=20)		Simvastatin (n=19)	
		Baseline	Post-treatment	Baseline	Post-treatment
Adiponectin	Low(n)	15	13	11	12
	Normal (n)	3	6	7	5
	High (n)	2	1	1	2
P value a		0.564		0.100	
P value b			0.420		
FI	Low (n)	13	13	14	10
	Normal (n)	5	3	1	5
	High (n)	2	4	4	4
P value a		0.564		0.102	
P value b			0.742		
HOMA-IR	Normal (n)	17	15	15	13
	Moderate (n)	1	3	1	2
	High (n)	2	2	3	4
P value a		0.157		0.180	
P value b			0.447		

Adiponectin level: Low = <3μg/mL, Normal = 3-30μg/mL, High = >30μg/mL;
Fasting insulin (FI) level: Low = <3μU/mL, Normal = 3-8μU/mL, High = >8μU/mL
HOMA-IR: Normal = 0.5-1.4 Moderate = 1.4-2.9, High = >2.9
[a] p-value between baseline and post-treatment; [b] p-value between atorvastatin and simvastatin group

antihypertensive agents, which were mostly prescribed in dual combination. Based on statistical analysis, the demography of both groups was not significantly different in all aspects.

Table 2 presents the mean levels of adiponectin, fasting insulin, and blood glucose in patients before and after being treated with atorvastatin or simvastatin. Although it was not statistically significant, adiponectin level was reduced by 30% in the atorvastatin group, but the fasting insulin and HOMA-IR index were unchanged.

Similar to that in the atorvastatin group, the mean levels of adiponectin and FBG in the simvastatin group were not significantly changed after treatment. Nonetheless, the simvastatin treatment was found to significantly increase the level of fasting insulin (p-value = 0.033). Although statistically not significant, the HOMA-IR value of simvastatin-treated patients increased by 44% post-treatment, which may have a significant clinical effect in terms of insulin resistance.

Table 3 shows the number of patients with low, normal, or high adiponectin levels. The normal plasma adiponectin level ranges from 3 to 30 μg/mL (22) and the normal fasting insulin levels were from 3 to 8 μU/mL. Fifteen out of 20 subjects (75%) in the atorvastatin group had initial low circulating adiponectin levels (<3 μg/mL), while only 3 subjects had normal and 2 had elevated circulating adiponectin. It is found that the 2 subjects who had distinctively high baseline adiponectin levels also had extremely high circulating insulin. Two-month atorvastatin treatment (20 mg/day) on these subjects led to a decrease in adiponectin levels by 29-60%, hence, resulting in normal adiponectin levels post-treatment.

Meanwhile, in the simvastatin group, 11 patients (58%) experienced low circulating adiponectin levels and 14 patients (73%) had low fasting insulin levels prior to treatment. Three subjects had normal adiponectin levels but the fasting insulin levels were considered elevated. After two months, 1 subject whose initial adiponectin levels were normal, experienced a significant increase in adiponectin levels following simvastatin treatment (20 mg/day).

Based on Spearman's rho correlation test, there was a significant correlation between adiponectin and fasting insulin levels in both groups, before or after treatments (Table 4). Although there was no correlation found between the FBG level and adiponectin, the HOMA-IR value was found to

Table 4: Correlation Between Adiponectin Levels and Other Variables Before and After Statin Treatment

Variables	Atorvastatin				Simvastatin			
	Baseline		Post-treatment		Baseline		Post-treatment	
	r	p	r	p	r	p	r	p
FBG	0.035	0.884	-0.053	0.824	0.115	0.640	-0.034	0.889
FI	0.507	0.023*	0.810	0.001**	0.829	0.001**	0.869	0.001**
HOMA-IR	0.508	0.022*	0.775	0.001**	0.831	0.001**	0.869	0.001**
Sex	-0.209	0.376	-0.139	0.558	0.107	0.663	-0.204	0.401
Age	-0.310	0.183	-0.309	0.185	0.201	0.409	0.179	0.463
BMI	0.100	0.674	0.041	0.862	0.265	0.273	0.285	0.238
PA	0.124	0.603	0.151	0.526	-0.136	0.578	-0.107	0.663

FBG: Fasting Blood Glucose; FI: Fasting Insulin; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance; BMI: Body Mass Index; PA Physical Activities; p-values based on Spearman's rho correlation test

significantly correlate with adiponectin levels in both groups.

Discussion

Based on the guideline on the management of blood cholesterol, statins are the first drug of choice in the primary and secondary prevention of atherosclerotic cardiovascular disease (23). The use of statins is recommended for groups of people with very high-risk future atherosclerotic cardiovascular disease (ASCVD) events and also for people with primary severe hypercholesterolemia (23). Statins have been known to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) by 15-37% (24). However, statins are reported to inhibit glucose metabolism by decreasing circulating adiponectin levels leading to reduced insulin sensitivity (15).

In this study, the subjects were recruited from dyslipidemic non-diabetic patients. The baseline adiponectin levels of the subjects were predominantly low (< 3 μg/mL), which is more likely due to the hypercholesterolemic condition of the subjects involved. Dyslipidemia is associated with low adiponectin levels even in non-diabetic patients (25). Nevertheless, it was found that 3 out of the total 39 dyslipidemic subjects had markedly high baseline adiponectin levels (>50 mg/L). In this present study, no significant correlation was found between the intensity of physical activity and BMI with adiponectin levels in non-diabetic patients. Unlikely, physical activities and BMI were found to correlate with glycemic controls in DM type 2 patients (26).

Another factor that may influence the elevation of adiponectin levels is the use of antihypertensive agents. Several antihypertensive agents have been reported to increase the level of adiponectin including ramipril and valsartan[27]. Apparently, a marked elevation of adiponectin level is not always beneficial, indeed, it has been associated with an increased risk of atrial fibrillation, especially in the elderly (28).

Intriguingly, different types of statin treatments may differently affect circulating adiponectin levels and the risk of glycemic disturbance. Following 2 months of treatments, atorvastatin use had led to a decrease in adiponectin levels by 32%, but it did not reach statistical significance. A similar finding was obtained by Koh and co-worker's study (2010), which also shows 20 that mg/day of atorvastatin led to an insignificant reduction of the adiponectin level in hypercholesteremic patients compared to the baseline (29). In contrast to atorvastatin, simvastatin treatment in this study has led to a rise in adiponectin level by 44%, a significant increase in the fasting insulin level ($p<0.05$), and a greater HOMA-IR index. This may indicate simvastatin treatment may lead to a progression of insulin resistance after two months, but not with atorvastatin treatment.

A meta-analysis study by Chrusciel et al. (2016) has confirmed that statin therapies, in general, can instigate a significant increase in adiponectin levels, but the authors suggest that the development of hyperglycemia in hypercholesteremic patients may not be related to statins' modulation on circulating adiponectin (30). Again, in this study, we observed a very significant correlation ($p<0.01$) between the fluctuation of the adiponectin levels and the

fasting insulin levels in both treatment groups. In the atorvastatin group, the adiponectin level was slightly reduced but the FBG, fasting insulin level, and the HOMA-IR index were not significantly modified after treatment. In contrast, simvastatin therapy caused a significant increase in fasting insulin levels simultaneously with an increase in adiponectin levels. It is postulated that different types of statins may elicit different effects on insulin sensitivity, which may relate to their effects on adiponectin levels. Further study with a greater sample size is warranted to be able to confirm this.

Simvastatin, but not atorvastatin, significantly increase the fasting insulin level, and HOMA-IR to a lesser extent, in non-diabetic dyslipidemic patients. The increased level of fasting insulin is significantly correlated with the increase in adiponectin level, suggesting that the two-month simvastatin use may stimulate insulin resistance in this population without reducing the plasma level of adiponectin.

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