

# Effect of Dyslipidemia Therapy on Creatinine Kinase Activity Level in Patients with Heart Disease

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## Effect of Dyslipidemia Therapy on Creatinine Kinase Activity Level in Patients with Heart Disease

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### ABSTRACT

Cardiovascular disease remains a significant health problem in the Asia Pacific region. Several studies have found that dyslipidemia is a cause of morbidity and mortality and requires high medical costs. Dyslipidemia is a risk factor for atherosclerosis. The most widely used therapy for dyslipidemia is statins. Statins often cause muscle disorders such as myalgia, myopathy, and rhabdomyolysis, which can cause death. A prospective cohort study design was carried out at Airlangga University Hospital, Surabaya, from April to November 2019. A total of 26 sample pairs containing 13 samples were treated with Atorvastatin, and 13 samples were treated with Simvastatin. The subjects were examined for the creatinine kinase activity level using enzymatic methods. The mean creatinine kinase levels in the atorvastatin group before and after treatment was 105.71 IU/L and 100.03 IU/L, respectively, because the subjects were diagnosed with acute coronary syndromes and blood was collected during acute conditions. Median creatinine kinase levels in the Simvastatin group were 85.5 IU/L before therapy and 118.1 IU/L after therapy, indicating significant differences in creatinine kinase levels before and after treatment. Simvastatin is very susceptible to certain drug interactions that can increase the concentration of statins in the serum. There were differences in levels of creatinine kinase activity before and after Simvastatin therapy but not Atorvastatin.

**Keywords:** Dyslipidemia, Atorvastatin, Simvastatin, creatinine kinase, enzymatic methods

### INTRODUCTION

Dyslipidemia is a metabolic disorder that causes an increase in plasma cholesterol and triglyceride concentrations. World Health Organization (WHO) estimated the prevalence of dyslipidemia in Southeast Asia (30.3%) and the Western Pacific (36.7%) was much lower than in Europe (53.7%) and America (47.7%) in 2008. The prevalence of dyslipidemia throughout the Asia Pacific region varies.<sup>1,2</sup>

Lifestyle modifications have been shown to lower serum cholesterol levels, with the most notable benefits from diet and weight loss in people at risk of atherosclerosis.<sup>3</sup> In addition to lifestyle changes, therapy for dyslipidemia using statins is also needed. Statins are known as the first treatment for hypercholesterolemia in 1987. The use of statin drugs continues to increase to more than 100 million prescriptions per year. Statins are anticholesterol drugs that are widely prescribed and successfully reduce the risks associated with cardiovascular disease. Side effects most commonly associated with

statin use include muscle cramps, muscle aches, muscle fatigue, muscle weakness, and muscle damage that can cause death.<sup>4</sup>

The National Lipids Association's (NLA) muscle expert panel and other statin experts in 2014 stressed the importance of standardization of statin therapy related to myopathy. Management is carried out in myopathy due to statins to stop statin therapy and rechallenge with the same statin therapy or other statin classes. Efforts are needed to provide uniformity in the diagnosis of muscular disorders. Therefore, conditions due to muscle disorders are classified into myalgia, myositis, rhabdomyolysis, and asymptomatic myopathy. A laboratory test of Creatine Kinase (CK) must be performed to distinguish these classifications in addition to the clinical symptoms.<sup>5</sup>

How Statin induces myopathy remains elusive, although several mechanisms have been proposed. One of the suspicions is that the disruption of cholesterol synthesis causes changes in the myocyte membrane in cholesterol and changes the myocyte membrane's behavior. Another mechanism is the

damage to the synthesis of compounds in the cholesterol pathway, especially deficiency of coenzyme Q10 (CoQ10, also known as ubiquinone), which causes disruption of enzyme activity in the mitochondria. Abnormal mitochondrial function with depletion of CoQ10 have been reported during statin therapy in asymptomatic patients.<sup>6</sup>

Creatine kinase is an enzyme present in tissue and energy-demanding cells, such as skeletal and cardiac muscles. It is considered the best marker for the detection and monitoring of skeletal muscle diseases.<sup>7</sup> The purpose of this study was to analyze anticholesterol therapy's effect on CK activity levels in patients with heart disease at Airlangga University Hospital, Surabaya.

## METHODS

This study used an analytical prospective cohort design performed on patients treated at the Emergency and Cardiac Outpatient Clinic. They checked their blood in the Clinical Pathology Laboratory of Airlangga University Hospital in Surabaya from April 2019 to November 2019. Measurement of CK activity levels was performed on heart patients treated with Atorvastatin and Simvastatin at least one month. The anti cholesterol therapy used was Atorvastatin, the maximum dose of 80 mg/day, and Simvastatin 40 mg/day, with a random treatment choice.

The CK activity level was measured at the Clinical Pathology Laboratory of Airlangga University Hospital. Criteria for acceptance of samples include age >18 years, heart disease patients (coronary artery disease, atherosclerosis, and hypertensive heart disease) who have not been treated with anticholesterol (Atorvastatin and Simvastatin) and were willing to sign informed consent. In contrast, the rejected sample was a hemolysis blood sample and patients with a history of muscle injury. Based on the calculation, the minimum sample size used by each group was ten samples. The study subjects included in this study were 13 samples in the Atorvastatin group and 13 in the Simvastatin group, which performed CK activity measurement twice before and after Atorvastatin and Simvastatin therapy. In this study, three patients dropped out because the patient died and did not the medication regularly. Diabetes Mellitus (DM) criteria by the American Diabetes Association (ADA) include the following: a Fasting Plasma Glucose (FPG) level of  $\geq 126$  mg/dL or a 2-hour plasma glucose level of  $\geq 200$  mg/dL during a 75 gram Oral Glucose Tolerance Test

(OGTT), or random plasma glucose of  $\geq 200$  mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or a hemoglobin A1c (HbA1c) level of  $\geq 6.5\%$ . Adult blood pressure classification according to the Joint National Community on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 7 (JNC 7) are normal (systolic < 120 mmHg and diastolic < 80 mmHg), pre-hypertension (systolic 120-139 mmHg or diastolic 80-89 mmHg), Grade 1 hypertension (systolic 140-159 mmHg or diastolic 90-99 mmHg), Grade 2 hypertension (systolic  $\geq 160$  mmHg or diastolic  $\geq 100$  mmHg).

The "optimized standard method" was used to measure CK activity levels in this study, according to recommendations from the German Society for Clinical Chemistry (Deutsche Gesellschaft für Klinische Chemie) with enzymatic principles. Samples were examined using a patient's serum of around 50  $\mu$ L; the serum can be stored at  $-20^{\circ}\text{C}$  so that the condition is stable for 30 days. Reagents by Human Diagnostic Worldwide and Humastar 100 devices made in Germany were used in this study for CK (NAC-act) activity level measurement.

The CK test examination is based on the CK enzyme's catalytic reaction between creatine phosphate and Adenosine Diphosphate (ADP) to creatine and Adenosine Triphosphate (ATP). The formed ATP and glucose will be catalyzed with the help of the hexokinase enzyme into Glucose-6-Phosphate (G6P). Glucose-6-phosphate will reduce Nicotinamide Adenine Dinucleotide Phosphate (NADP) to NADPH with the help of the enzyme Glucose-6-phosphate dehydrogenase. The reduction of NADP to NADPH is measured as an increase in the sample's absorbance, proportional to the CK activity in the model.

A numerical data scale was used to analyze the data distribution, and a T-paired test was used for data with a normal distribution. In contrast, the Wilcoxon rank test was used for data with a normal distribution. A p-value < 0.05 with a 95% Confident Interval (CI) was considered as a significant result.

This study was approved by the Airlangga University Hospital Research Ethics Committee with number 180/KEP/2019. All research subjects were asked for approval by signing a written informed consent.

## RESULTS AND DISCUSSION

This study's sample size was 52, consisting of 26 samples before statin therapy and 26 samples after

statin therapy. Twenty-six samples before statin therapy consisted of 13 samples before Atorvastatin therapy and 13 samples before Simvastatin therapy. Twenty-six samples after statin therapy consisted of 13 samples after Atorvastatin therapy and 13 samples after Simvastatin therapy for at least one month. This number has met the sample size determined in this study. Other drugs used in this study were Nifedipine, Amlodipine, Aspirin, Concor, Candesartan. Research subjects as the inclusion criteria consisted of coronary artery disease, atherosclerosis, and hypertensive heart disease. Research subjects were treated at the Emergency and Cardiac Outpatient Clinic, who checked their blood in the Clinical Pathology Laboratory of Airlangga University. The study subjects' characteristics in this study, including gender, age, DM, hypertension, and smoking, are shown in Table 1.

Based on gender, there were 11 (84.6%) male and 2 (15.4%) female subjects in the group treated with Atorvastatin. The group treated with Atorvastatin had a diagnosis of coronary artery disease. In this group, there were two patients with a diagnosis of coronary artery disease with DM. Coronary artery disease is a disease that frequently causes death and disability throughout the world. This study found that the number of Acute Coronary Syndrome (ACS) patients was more common in males than in females. The incidence of acute coronary events is higher in males than females. This fact was consistent with Lu *et al.* in Malaysia and Muhibbah *et al.* in Banjarmasin, which showed that ACS patients were more common in males than females. The tendency for ACS is more significant in older females (post-menopause). The possibility of sex-specific pathophysiology of ACS may explain some of the differences in the manifestation of symptoms between males and females. Although chest pain is the most common ACS symptom in both males and females, presentation without chest pain or with atypical

symptoms is more frequent among females. Compared to males, females were older and had significantly more comorbidities such as DM, hypertension, and dyslipidemia. Diabetes mellitus is especially prevalent in young females with ACS.<sup>8,9</sup>

More female subjects were found in Simvastatin's group by ten people (76.9%) than three male (23.1%) subjects. The diagnosis in the group treated by Simvastatin was dominated by hypertensive heart disease. The incidence of hypertensive heart disease is more common in females over 50 years than males. The difference in blood pressure between females and males is multifactorial and is not fully understood. There are several hypotheses in post-menopausal females as the potential role of sex hormones, the Renin-Angiotensin System (RAS), oxidative stress, weight gain, and activation of sympathetic nerves in post-menopausal hypertension.<sup>10</sup>

The mean age in the Atorvastatin and Simvastatin groups was 57.5±9.9 years and 57.7±15.8 years, indicating no significant difference. Atorvastatin group with ACS diagnosis was more common in people over 50 years of age. This finding was following Mirghani research at the Sudan Hospital, which assesses the age difference, therapy, and complications in patients with ACS. It is said that ages over 50 years are more at risk of developing ACS. The vulnerability of an ACS increases with age. Age is a risk factor for ACS that cannot be modified.<sup>11</sup> Research subjects in the Simvastatin group over 50 years of age. The mean age of subjects in the Simvastatin group in this study was 57.7±15.8 years. It was consistent with Nkoke *et al.* showing that there were 43.2% of hypertensive heart disease with an average age of 58 years.<sup>12</sup>

The duration of drug consumption in the Atorvastatin and Simvastatin groups was 41±5.6 days and 37±9.8 days, with Mann-Whitney test results showing significant differences. The

**Table 1.** The characteristics of subjects

Characteristics of Subjects	Group		Total (n=26)	p-value
	Atorvastatin (n=13)	Simvastatin (n=13)		
<b>Gender (n, %)</b>				
Male	11 (84.6%)	3 (23.1%)	14 (53.8%)	0.006
Female	2 (15.4%)	10 (76.9%)	12 (46.2%)	
<b>Age (years)</b>				
Mean (standard deviation)	57.5 (±9.9)	57.7(±15.8)	57.6(±12.9)	0.965
Diabetes mellitus (n, %)	2 (15.4%)	0 (0%)	2 (7.7%)	0.480
Hypertension (n, %)	8 (61.5%)	13 (100%)	21 (80.8%)	0.039
Smoking (n, %)	11 (84.6%)	3 (23.1%)	14 (53.8%)	0.006



Simvastatin group's distribution was not evenly distributed, with the most prolonged drug consumption was 62 days long.

Risk factors in this study were DM, hypertension, and smoking. Based on analysis with the Chi-Square test, no significant differences were found for risk factors for DM, while significant differences of hypertension and smoking were found with  $p < 0.05$ . Diabetes mellitus, hypertension, and smoking are modifiable risk factors. As one of the life-threatening risk factors for patients with cardiovascular disease, DM is easily diagnosed.<sup>13</sup> Diabetes mellitus is an independent risk factor for ACS. The mortality rate of ACS patients with DM is higher than ACS patients who do not suffer from DM. It is because these patients tend to experience prothrombotic, which can cause plaque rupture.<sup>14</sup> Diabetes mellitus is associated with macrovascular (involving large arteries) and microvascular (involving small arteries and capillaries) disorders. Chronic hyperglycemia and insulin resistance play an essential role in the initiation of vascular complications of diabetes.<sup>13</sup> Hypertension in heart disease is a modifiable risk factor. Hypertension is a risk factor for most cardiovascular diseases (including coronary heart disease, left ventricular hypertrophy, heart valve disease, cardiac arrhythmias including atrial fibrillation) and cerebral stroke and kidney failure.<sup>15</sup>

The Atorvastatin group diagnosed with ST-Elevation Myocardial Infarction (STEMI) in this study had risk factors for smoking. Smoking is significantly associated with ACS, especially STEMI. It was suggested that smoking is also an established risk factor for Ischemic Heart Disease (IHD), and nearly 30% of all deaths from ACS are caused by smoking.<sup>16</sup>

The differences in CK activity levels in patients before and after being treated with Atorvastatin were analyzed by a T-paired test, as shown in Table 2. The study subjects showed no significant differences in the average levels of CK activity before and after treatment with Atorvastatin ( $p > 0.05$ ).

The majority of subjects receiving Atorvastatin therapy were ACS. The mean CK activity level before treatment was higher than after treatment with Atorvastatin. This fact was because blood serum was taken during an acute condition. It was shown that no significant difference in CK activity levels was found before and after therapy with Atorvastatin.

Most of the Atorvastatin group subjects had higher levels of CK activity before treatment than after treatment. Total CK activity levels in the blood emerge within 3-9 hours after acute myocardial infarction, reaching a maximum value in 10-20 hours, and its activity returns to average around 72 hours. The sensitivity of CK biomarkers was very high after the onset of symptoms of coronary disease. Danese and Montagnana's study reported that the sensitivity of CK was 98% when blood was collected within 72 hours.<sup>17</sup> This result was following this study, where the average obtained before therapy was higher than after treatment. Morales *et al.* assessed CK levels and muscle strength before and after treatment. Univariate analyses were used to compare CK levels between the Atorvastatin and placebo groups. Repeated measures were performed to evaluate the relationship between change in CK and measurements of muscle strength. This study showed more subjects on high dose Atorvastatin treatment increased their CK greater than twice their baseline CK value and increased their CK  $> 20$  U/L.<sup>18</sup> Contrastingly,

**Table 2.** Difference analysis of CK activity levels in patients with heart disease before and after treatment with Atorvastatin

Variable	Mean ± Standard Deviation	p-value
<b>CK activity</b>		
Before therapy with Atorvastatin	105,71 ± 62,306	0.738
After therapy with Atorvastatin	100,03 ± 68,114	

T-paired test, p-value  $< 0.05$  was significant

**Table 3.** Difference test results of CK activity levels in cardiac patients before and after treatment with Simvastatin

Variable	Median	p-value
<b>CK activity</b>		
Before therapy with Simvastatin	85.5 (49.7–260,2)	0.046
After therapy with Simvastatin	118,1 (48.6–206,7)	

Wilcoxon test, p-value  $< 0.05$  was significant

this study showed a decrease in mean levels of CK activity after therapy, although not significantly different. This result might be due to a lower dose of Atorvastatin, 20 mg/day.

Table 3 shows the Wilcoxon test results to determine the difference in CK activity levels in patients before and after treatment with Simvastatin. The cardiac patients treated with Simvastatin in this study were 13 subjects. The analysis showed that 12 (92.3%) subjects had increased CK activity levels after treatment with Simvastatin, and 1 (7.7%) subject had increased CK activity levels before treatment with Simvastatin.

Female subjects with hypertensive heart disease dominated the diagnosis of subjects in the group treated with Simvastatin. The dose of Simvastatin used was 20 mg daily. The results of CK activity levels measurement before therapy were lower than after Simvastatin therapy. The study results showed a significant difference in CK activity level before and after treatment with  $p < 0.05$ .

Simvastatin is a hypercholesterolemia drug that is often prescribed and one of the statins with moderate potentiation. This therapy is intended to reduce cardiovascular events and death in high-risk patients. This study shows that Simvastatin is more at risk of causing side effects to the muscles than other statins, especially when the treatment is combined with cytochrome P450 isoenzyme inhibitors. In this group, most were combined with cytochrome P450 inhibitor (Nifedipine and Amlodipine). Simvastatin is very susceptible to specific drug interactions that can increase the concentration of statins in serum and increase myopathy risk.<sup>19</sup>

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) demonstrated a dose-effect on the development of myopathy, where 80 mg daily of Simvastatin produced a 10-fold higher rate than a 20 mg dose or the 40 mg used in the Heart Protection Study (HPS), with risk higher when it occurred in combination with elevated CK levels.<sup>20</sup>

The limitations of this study were a selection of subjects in the study included patients with ACS, duration of consumption of dyslipidemia therapy 1-3 months.

## CONCLUSION AND SUGGESTION

Based on this study, it was concluded that there were no differences in CK activity levels before and after therapy with Atorvastatin. At the same time, there were significant differences in CK activity levels

in the group of patients treated with Simvastatin with  $p < 0.005$ . Further research was needed by limiting subjects from diseases that can increase CK levels, such as acute coronary syndrome, decreased kidney and liver function, and a longer observation time.

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# Effect of Dyslipidemia Therapy on Creatinine Kinase Activity Level in Patients with Heart Disease

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GRADEMARK REPORT

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GENERAL COMMENTS

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