

# Simvastatin Effect on High-Sensitivity C-reactive Protein in Type 2 Diabetes Mellitus

*by Agung Pranoto*

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## Simvastatin Effect on High-Sensitivity C-Reactive Protein in Type 2 Diabetes Mellitus

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### ABSTRACT

Cardiovascular disease (CVD) as a complication of type 2 diabetes mellitus (T2DM) is associated with chronic low-grade inflammation. Statin has an anti-inflammatory effect that is marked by decreasing inflammatory marker, such as high-sensitivity C-reactive protein (hsCRP). This study aims to evaluate the administration of simvastatin in influencing hsCRP level in patients with T2DM. A randomized control study involving subjects with T2DM which divided into two groups was conducted. Pre- and post-treatment measurements of lipid profile, HbA1c, hsCRP were performed in both groups. Triglyceride and HbA1c levels were significantly different between two groups ( $p=0.001$ ,  $p=0.016$ , respectively). Only HbA1c was significantly associated with pre-treatment hsCRP level ( $p=0.006$ ). After three months, statin group showed significantly lower hsCRP level than that before treatment

( $p=0.002$ ). Moreover, pre- and post-treatment differences of hsCRP level in both groups were also significant ( $0.41\pm 0.26$  vs  $-0.13\pm 0.32$ , respectively,  $p=0.003$ ). Simvastatin could reduce inflammation in T2DM patients that was marked by decreasing level of hsCRP.

**Keywords:** simvastatin, high-sensitivity C-reactive protein, type 2 diabetes mellitus, inflammation

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### INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is rising. T2DM is one of the main causes of increasing global health morbidity and mortality for diabetes cases.(1) In 2010, 6.6% of the world population (285 million) was suffered from this disease, and it is predicted to reach 438 million people in 2030. One of the most serious complications of T2DM is cardiovascular disease (CVD)(2) that contributes to 50% mortality of patients with T2DM. The relative risk of mortality caused by coronary artery disease among men and women with T2DM is 1.5-2.5 times higher and four times higher than subjects without T2DM.(3,4)

Chronic low-grade inflammation is a basic feature of T2DM, either in the pathophysiological process or in complication development.(5,6) Chronic low-grade inflammation is associated with atherosclerosis, the initial cause of CVD.(7) The atherosclerosis risk factors explain just of a minor part of the excess incidence of vascular disease among T2DM.(8) Therefore, control of inflammation is important to prevent diabetes-related CVD. One of the biomarkers that can be used as early predictor of CVD is high-sensitivity C-reactive protein (hsCRP).(6) A study in Bangladesh showed that hsCRP level in normal subject was 0.93 mg/L, while in subjects with T2DM ranged between 1.13-3.86 mg/L, higher than the lower level of cardiovascular risk (1 mg/L).(9-11)

The role of hsCRP in T2DM natural course is still controversial, either as a biomarker alone or involved in the development of atherosclerosis. Current evidence shows that hsCRP enhances monocyte recruitment in the formation of atheromatous plaque, induces endothelial dysfunction by inhibiting nitric oxide (NO) release, and induces plasminogen activator inhibitor-1 (PAI-1) as well as other adhesion molecules to regulate macrophage LDL absorption. However, the lack of study about hsCRP inhibition makes that evidence is still controversial. Therefore, the reduction of hsCRP level is not only associated with reduction in CVD risk but also reduces inflammation as the primary cause of atherosclerosis.(12)

Statin is known not only as anti-dyslipidemia but also anti-inflammatory agent, but statin is not routinely prescribed for T2DM without dyslipidemia. Its prescription is expected to reduce inflammation that characterized by decreasing hsCRP level and eventually reducing CVD risk. Our study evaluated the administration of simvastatin, a widely available and inexpensive statin, in influencing hsCRP level in patients with T2DM.

### METHODOLOGY

A single blinded, randomized control trial study was performed in Dr. Soetomo General Hospital, Surabaya. Thirty-two subjects with T2DM and dyslipidemia according to criteria of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)(13) and American Diabetes Association clinical criteria(14) who routinely visit diabetic clinic were involved in this study. Subjects who consumed antihypertensive agent, had history of smoking, trauma, autoimmune disease, trauma, as well as their HbA1c >9%, LDL <100 mg/dL, and triglyceride >500 mg/dL were excluded from this study. Five subjects were dropped out because of poor compliance or they consumed another drug. All subjects signed the informed consent, and this study was approved by the Health Research Ethics Committee of Universitas Airlangga.

The subjects of this study were divided into two groups. One group was as group who consumed 20 mg simvastatin once daily for three months, and the other was as control group who consumed placebo. We used generic simvastatin tablet (Kimia Farma Indonesia) in aluminium blister that labeled as "drug" as well as placebo. Level of hsCRP was measured from venous blood using immunoturbidimetric assay (Cobas C 501 analyzer). Cardiac C-reactive protein (latex) high sensitive (CRPHS) was obtained from Roche. The significance of differences between pre- and post-treatment in both groups were assessed by using paired t test or Wilcoxon sign rank test based on data normality.  $P < 0.05$  is considered significant.

## RESULTS

The baseline demographic, BMI, lipid profile, and glycemic control of both groups are shown in Table 1. The mean age of the subjects in statin and control group was  $59 \pm 9.174$  and  $61,14 \pm 7.941$ , respectively. No significant differences were found between two group except for triglyceride and HbA1c level ( $p = 0.001$ ,  $p = 0.016$ , respectively). Pre-treatment hsCRP level between both groups did not show significant difference but showed significant correlation with HbA1c level ( $p = 0.006$ ).

Change of hsCRP level before and after treatment in both groups is shown in Figure 1. hsCRP level in statin group tended to decrease but increased in control group. Pre- and post-treatment hsCRP level was significantly difference in statin group ( $p = 0.002$ ), but not in control group ( $p = 0.159$ ). Comparison of pre- and post-treatment value difference between statin group and control group was also significant ( $0.41 \pm 0.26$  vs  $-0.13 \pm 0.32$ , respectively,  $p=0.003$ ) (Figure 1).

## DISCUSSION AND CONCLUSION

We found triglyceride and HbA1c level were significantly different between two groups. Also, HbA1c was correlated with pre-treatment hsCRP level. Moreover, this study showed that simvastatin administration could significantly reduce hsCRP level in subject with T2DM.

Several studies have concluded that hsCRP is a strong predictor of cardiovascular disease (CVD).<sup>(15–18)</sup> The precise mechanism by which CRP may be correlated with CVD remains uncertain. Initially, it is considered just as a biomarker of inflammation in CVD pathogenesis, but recent evidence shows that CRP has a direct causative role of atherosclerosis. hsCRP is considered as a biomarker of inflammation because its production is induced by IL-6 released from uptake of oxidized LDL within arterial atheromatous plaque, from adipose tissue, or other site of chronic infection.<sup>(19)</sup> Recent evidence shows that hsCRP also plays an important role in different steps of atherogenesis development. It contributes in atherogenesis progression by exerting pro-inflammatory effect, modulating the innate immune response, activating complement system, promoting platelet activation, thrombus formation, vascular remodeling, and angiogenesis.<sup>(20)</sup>

This study found no correlation between hsCRP level and pre-treatment lipid profile. Correlation of hsCRP level and lipid profile is controversial. Study by Dongway<sup>(21)</sup> showed that hsCRP in patients with T2DM and artery coronary disease was only significantly correlated with LDL-C. Whereas, Wali & Patil<sup>(22)</sup> showed that hsCRP level was correlated with all parameter of lipid profile. The data discrepancy between studies perhaps was caused by different characteristic of subjects involved in each study. BMI in our study was lower than those in two previous studies ( $29.45 \pm 2.66$  and  $28.4 \pm 4.1$ , respectively). Previous study has conclude that BMI  $\geq 25$  was positively correlated with total cholesterol, LDL, triglyceride, but negatively correlated with HDL.<sup>(23)</sup>

We also found that HbA1c was correlated with hsCRP level. High HbA1c is a biomarker for poor glycemic control high risk for complications.<sup>(24)</sup> Thus, high HbA1c should trigger inflammation. Monitoring of this marker is essential in the clinical management of T2DM because dyslipidemia is well-known risk factors of atherosclerosis and is common in diabetic patients.<sup>(25)</sup> Previous study has conclude that HbA1c level and hsCRP level had positive significant correlation in patients with T2DM,<sup>(26)</sup> as well as in non-diabetic subjects.<sup>(27)</sup> Another study showed that hsCRP in the T2DM patients with HbA1c  $\geq 7\%$  was higher than in the patients with HbA1c  $< 7\%$ , but not statistically significant.<sup>(28)</sup> Knowledge of molecular mechanism shows possible causality between of hsCRP and HbA1c. Tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6) are over expressed in adipose tissue of person with obesity. These pro-inflammatory cytokines stimulate production of CRP in liver and induce insulin resistance, which, in turn, cause hyperglycemia and elevation of HbA1c.

Statin (3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors) is widely used in prevention of CVD not only because its cholesterol lowering properties but also its pleiotropic properties, such as anti-inflammation. Our study showed that simvastatin administration could significantly reduce hsCRP level in subject with T2DM. Previous studies also showed similar finding either in subjects with or without T2DM patients.<sup>(29–31)</sup> Statin could reduce hsCRP level by reducing inflammation within artery, possibly by reducing amount of LDL available for oxidative metabolism and reducing production and/or circulation of mediators such as TNF- $\alpha$  and IL-6, and leukocyte function antigen-1.<sup>(19)</sup> Inhibition of CRP expression is mediated by inhibition of transcription factor STAT3. However, the data are based on in vitro study of tissue culture.<sup>(32)</sup> Study in human CRP metabolism showed that statin reduced CRP level by enhance its fractional catabolite rate.<sup>(33)</sup>

We did not find another study that has similar methods as our recent study. One study in subject with elevated LDL cholesterol without T2DM who consumed simvastatin for 14 days was also experienced reduction in CRP level.<sup>(19)</sup> However, not all study concluded that reducing hsCRP could also reduce risk for CVD development. Collaborative Atorvastatin Diabetes Trial (CARDS) and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study did not supported the idea of statin administration to reduce CRP level as an attempt to reduce CVD risk.<sup>(29,31)</sup> The explanation for this finding is that other risk factors such as high triacylglycerol levels, low HDL-cholesterol levels, hypertension, and hyperglycemia partially mask the role of CRP as a risk factor for CVD development. Different type of statin used and subjects' characteristics could also influence the finding.

The role of measuring hsCRP as a method to identify healthy individuals who are at risk for CVD and to get benefit from statin therapy remains controversial. Another study has shown benefit of statin therapy on healthy individual who has elevated hsCRP ( $\geq 2$  mg/L).<sup>(30)</sup> However, the study had some limitation. First, the benefit of statin therapy on incidence reduction was modest. Second,

baseline levels of hsCRP did not predict benefit. Third, it remains unclear that inflammation is the mechanism through which statins work.(34) Several study also found that the use of statin in healthy and T2DM high risk subjects could increase by 12-30%, risk for developing T2DM through unclear mechanisms.(35,36) Despite these data show that statin could cause harm, Indonesian endocrinologist consensus on T2DM management still recommends statin prescription for T2DM patients who have CVD risk factors.(37)

Our recent study had some limitations. First, we used relatively small sample size. Second, we did not measure post-treatment lipid profile. Third, we did not perform cohort study, so we could not investigate whether hsCRP level is associated with CVD risk reduction. Then, a large sample size cohort study should be performed. Further development of a specific anti-CRP therapy is needed to precisely explain direct pathogenic role of CRP on CVD and to get better attempt to prevent CVD in T2DM patients as well as other high risk patients. Vascular inflammatory marker CRP levels are affected by various factor, such as BMI, trigliserida, and infections.(38)

In conclusion, this study showed that simvastatin administration could reduce inflammation in patients with T2DM that was marked by decrease level of hsCRP. Pre- and post-treatment differences of hsCRP level in both groups were significant.

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FIGURES

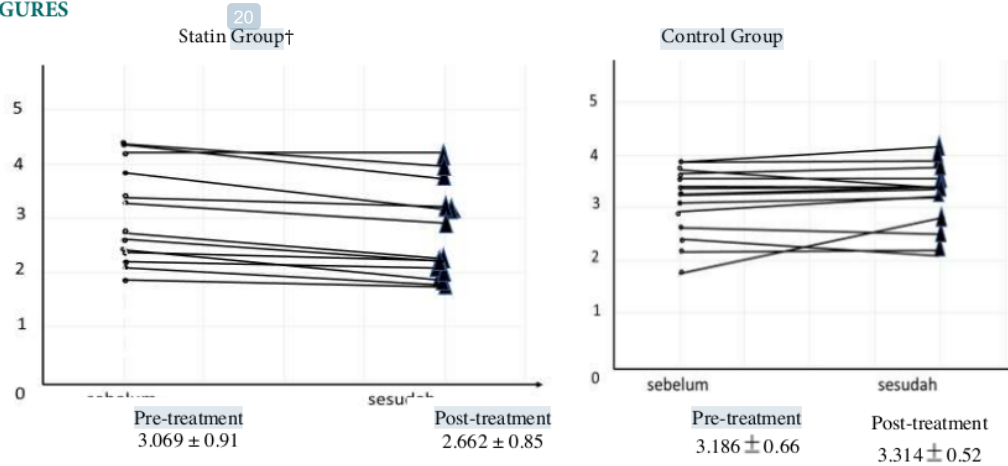


Figure 1. Pre- and post-treatment changes of hsCRP level and mean value of each group (mean ± SD mg/dL). Venous blood hsCRP level was measured using immunoturbidimetric assay. Mean value of hsCRP level pre- and post- treatment in statin group was significantly difference (p=0.002), but not in control group (0.159).

TABLES

Table 1. Characteristics of subjects, lipid profile, glycemic control, and its correlation to hsCRP level.

Parameters	Statin Group* n = 13	Control Group* n = 14	Comparison between group (p)	Correlation to hsCRP level (p)
Age (year)	59 ± 9.174	61.14 ± 7.941	0.585	0.526
BMI (kg/m <sup>2</sup> )**	26.807 ± 3.481	25.98 ± 2.76	0.506	0.565
Total Cholesterol (mg/dL)	198.08 ± 33.61	196.80 ± 28.37	0.915	0.057
Triglyceride (mg/dL)	246.31 ± 64.32	162.93 ± 48.69	0.001*	0.540
HDL-C (mg/dL)	39.38 ± 7.19	43.21 ± 11.26	0.307	0.697
LDL-C (mg/dL)	153.54 ± 28.34	128.71 ± 16.61	0.100	0.670

HbA1c (%)	7.88 ± 0.72	8.57 ± 0.66	0.016*	0.006*
hsCRP (mg/dL)	3.07 ± 0.91	3.19 ± 0.6	0.706	-

Data were provided as mean ±SD, BMI (body mass index), HDL-C (high-density lipoprotein – cholesterol), LDL-C (low-density lipoprotein – cholesterol), and hsCRP (high-sensitivity C-reactive protein), \*statistically significant (p<0.05)

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GENERAL COMMENTS

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