

## Correlation of Serum Sclerostin Levels with Carotid Intima Media Thickness in Chronic Kidney Disease Patients with Hemodialysis

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### Abstract

Chronic kidney disease is associated with high mortality rates mainly to cardiovascular disease related with mineral and bone disorders. Sclerostin is an inhibitor of Wnt signaling which has the effect of increasing vascular calcification in patients with chronic kidney disease. There are several studies that show different results. Carotid intima media thickness ultrasound examination is a tool to identify atherosclerosis which is part of vascular calcification. The purpose of this study is to look at the correlation of sclerostin with carotid intima media thickness (CIMT) in patients with chronic kidney disease undergoing maintenance hemodialysis. In this cross-sectional study, the sclerostin concentration was measured by an enzymed linked immunosorbent assay. CIMT measurement by ultrasound mode B examination. There were 40 patients in this study. The mean sclerostin level was  $256.68 \pm 127.76$  pg / ml. Sclerostin levels are considered high above 162 pg / ml, there are 30 people. CIMT thickening was present in 11 patients. There was no significant correlation of serum sclerostin with CIMT in patients with chronic kidney disease undergoing maintenance hemodialysis ( $r=0.32$   $p>0,847$ ). In multivariate linear regression, hemodialysis vintage is an independent factor that is significantly significant with CIMT. There was no significant correlation of serum sclerostin with CIMT in patients with chronic kidney disease undergoing hemodialysis.

Keywords: sclerostin, carotid intima media thickness, hemodialysis vintage

## **Introduction**

Chronic kidney disease is associated with a high mortality rate mainly associated with cardiovascular disease. The cause of the increased risk of cardiovascular disease is related to mineral and bone disorders that occur in chronic kidney disease. In bone mineral disorders (GMT) that occur starting in stage 3 chronic kidney disease include such as hyperphosphatemia, vascular calcification which is a new risk factor for cardiovascular disease.<sup>1</sup> Several studies have shown that chronic kidney disease reactivates a nephrogenesis development program that stimulates the kidney repair process. Signals that arise due to the kidney repair process are reactivation of the Wnt pathway that controls tubular epithelial proliferation and polarity during nephrogenesis. In addition there are Wnt inhibitors that function for Wnt autoregulation such as Sclerostin, Dickkopf-1, soluble frizzles related protein, Activin. In vascular calcification in bone mineral disorders in chronic kidney disease there is an increase in Wnt signal which causes an increase in bone formation in blood vessels resulting in an increase in sclerostin which inhibits bone formation. There is a systemic effect due to an undesirable increase in the level of excessive sclerostin, an increase in bone resorption. There are different research results on studies of the relationship of sclerostin with vascular and cardiovascular calcifications in chronic kidney disease. On the one hand there are studies that show that serum sclerostin values are associated with cardiovascular events in patients with chronic kidney disease such as Kanbay et al's study which shows serum sclerostin values are associated with cardiovascular events in populations of chronic kidney disease that have not yet performed dialysis.<sup>3</sup> The Ishimura et al study showed expression of strong sclerostin close to the area of vascular calcification and aortic valve.<sup>4</sup> Kirkpantur et al's study concluded that high sclerostin levels were associated with vascular calcification in patients with chronic kidney disease undergoing hemodialysis.<sup>5</sup> On the other hand there are studies that show the opposite results such as that of Yu Yang and his colleagues showing that the value of serum sclerostin levels is inversely related to vascular calcification and cardiovascular

events.<sup>6</sup> Dresclher and colleagues' studies mention high serum sclerostin levels associated with short-term cardiovascular mortality lower in dialysis patients.<sup>7</sup> This difference led researchers to study the relationship of serum sclerostin levels with vascular calcification in which case the carotid intima media thickness was examined. If there is a role of sclerostin in increasing the incidence of vascular calcification in patients with chronic kidney disease can be given anti sclerostin therapy which is expected to reduce vascular calcification and morbidity and mortality in patients with chronic kidney disease. Research that addresses this has never been done in the South Sumatra region in particular.

### **Methods**

The study design was an observational study with a cross sectional approach. The research subjects were patients undergoing hemodialysis at RSUP Dr. Moh Hoesin Palembang. Sclerostin levels were assessed by the ELISA method, which was carried out at the Biotechnology Laboratory, Faculty of Medicine, Sriwijaya University, Indonesia. Data analysis using IBM SPSS version 24 software with univariate and bivariate analysis.

### **Results**

The research subjects consisted of 27 men and 13 women. The duration of chronic kidney disease suffered by research subjects is a median of 3.5 years, a minimum of 1 year, a maximum of 15 years. The length of median hemodialysis is 12 months, minimum 3 months, maximum 120 months. Median body mass index (BMI) 23.6 normal, minimum 16.8, maximum 35.6. In this study the most common cause of CKD was hypertension of 12 people (30.8%), followed by diabetes mellitus of 11 people (28.2%), glomerulonephritis 7 people (17.9%), obstructive uropathy 3 (7.7%), hypertension and diabetes mellitus in 5 people (15.4%). Examination of carotid intima media thickness (CIMT) showed CIMT thickening in 11 people (27.5%), not thickening 29 people (72.5%). In this study, a positive correlation was obtained with

weak triglycerides and thickening of the carotid intima media thickness (CIMT) ( $r$  0.3  $P$  0.049). Whereas other risk factors such as age, diabetes hypertension, LDL levels were not correlated with carotid intima media thickness (CIMT). In chronic kidney disease and hemodialysis time, there is a weak positive correlation with thickening of carotid intima media thickness (CIMT) ( $r$  0.3  $P$  0.02). There is a weak negative correlation between serum sclerostin and carotid intima media thickness (CIMT) which is statistically not significant. From the results of multivariate analysis of linear regression analysis it was found that the length of hemodialysis as an independent factor associated with carotid intima media thickness (CIMT) thickening.

## **Discussion**

In this study chronic kidney disease duration and hemodialysis duration showed a weak positive correlation with thickening of the carotid intima media thickness (CIMT) ( $r$  0.3  $P$  0.02). This is consistent with Damjanovic et al's research in which there is a relationship between dialysis duration and vascular calcification and studies from Jasani and friends in the Indian population undergoing hemodialysis.<sup>8-11</sup> In contrast to the studies of Aiqun et al, Kirkpantur et al who stated there was no relationship between hemodialysis time with CIMT thickening.<sup>5,12</sup> Differences can be caused by heterogeneous populations that differ between studies such as comorbid diseases, drugs taken, different number of samples. In this study, a positive correlation was obtained with weak triglycerides and thickening of the carotid intima media thickness (CIMT) ( $r$  0.3  $P$  <0.05). In accordance with the research of Pencak et al, Lahoti et al.<sup>13-15</sup> In contrast to the research of Kirkpantur et al, Hinderliter et al, Kuswardhani et al where no correlation was found between triglycerides and CIMT thickening.<sup>16-18</sup> In sclerostin, there is a weak negative correlation that is not significant with carotid intima media thickness (CIMT), ie the higher the sclerostin level, the lower the carotid intima media thickness. In accordance with the research, the result is a negative correlation between sclerostin levels and vascular calcifications, such as

Yang et al. While the research of Tzung et al, Delaney et al found no significant relationship between serum sclerostin levels and vascular calcification.<sup>19-22</sup> However these results are different from other studies such as Kirkpantur et al. intima media thickness.<sup>5,23</sup>

Differences in results from various studies can be caused by the number of different samples such as small samples. In this study a sample of 40 people in the study of Aiqun et al 84 people, research Kirkpantur et al 122 people, research Jean et al 207 pasien, research 125 patients. Heterogeneous patients for example the difference in the age distribution of patients in this study the average age of  $49.9 \pm 12.98$  while the study of kirkpantur et al  $55 \pm 13$ . And the age distribution is uneven where there are 77.5% of age under 60 years, the rest above 60 years while in more studies are 60 years old. According to several studies that serum sclerostin levels have a relationship with age.<sup>22,61</sup> Differences in the number of comorbid compositions in research subjects such as diabetes mellitus and hypertension, differences in the length of time undergoing dialysis can also lead to different research results.<sup>5,25</sup> In the laboratory results of research subjects obtained high sclerostin results of 32 people (80%) above 162 pg / ml and 8 people (20%) below 162 pg / ml. Values above 162 pg / ml are considered high based on previous research.<sup>26</sup> Of 32 people who had high serum sclerostin levels 9 had CIMT thickening out of all 11 who had CIMT thickening. Cause there are not many study subjects who experience CIMT thickening (11 people who have CIMT thickening from a total of 40 study subjects) can be caused by phosphate and calcium levels in the study subjects are mostly normal. And parathyroid hormone levels are also mostly normal (only 42% are high). Based on the literature that hyperphosphatemia, hypercalcemia and hyperparathyroid can increase the risk of atherosclerosis and arteriosclerosis in CKD patients. Where has happened or not atherosclerosis and arteriosclerosis conditions can be seen from the thickening of CIMT.

Sclerostin itself is a glycoprotein involved in bone metabolism. Sclerostin is produced by osteocytes from the SOST gene and is a key molecule to inhibit osteoblast

activity. Sclerostin will inhibit Wnt  $\beta$  catenin pathway which is an important signal in osteoblastogenesis. Wnt  $\beta$  catenin pathway will trigger osteoblast differentiation and inhibit osteoclasts. Sclerostin will inhibit bone formation process. Sclerostin is considered to be a link between bone, kidney and vascular. There are still several differences of opinion about the role of sclerostin in vascular calcification in bone mineral disorders in CKD patients. Sclerostin as an antagonist of bone formation can inhibit vascular calcification through the same mechanism in bone. Seen from several studies that show high levels of sclerostin associated with decreased vascular calcification so that in some studies seen a negative correlation between sclerostin and vascular calcification.<sup>26-28</sup>

### **Conclusion**

In this study there was no significant correlation between serum sclerostin and carotid intima media thickness (CIMT) in patients with chronic kidney disease undergoing hemodialysis.

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