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# Association Between Serum Sclerostin Level and Carotid Artery Atherosclerosis in Hemodialysis Patients

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## ABSTRACT

**Introduction:** Sclerostin (an antagonist of Wnt/β-catenin signaling pathway) represents a novel candidate glycoprotein involved in the pathogenesis of low bone turnover and vascular calcification e.g. atherosclerosis in CKD patients (CKD-MBD). Measurement of carotid artery intima-media thickness (CIMT) by ultrasonography is a widely used and reliable imaging modality for the detection of subclinical atherosclerosis (increased CIMT). We investigated the association between serum sclerostin level and carotid artery atherosclerosis in hemodialysis patients. **Methods:** Our case-control study include 150 dialysis patients and 50 controls, serum sclerostin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA). CIMT was measured and carotid plaques were identified by carotid duplex. **Results:** There was a statistically significant difference (p-value <0.001) in sclerostin levels between cases (83.5±27.1pmol/L) and controls (26.3±5.8 pmol/L) with mean among cases ~3 times higher than controls. A significant positive correlation (p-value <0.001) exists between sclerostin levels and each of CIMT (r = 0.56) and plaques size (r = 0.53). Sclerostin levels were higher in patients with increased CIMT (77.6±17.8 pmol/L) than with normal CIMT (70.9±9.6 pmol/L) and the highest mean was among patients with plaque formation (109.3±35.1 pmol/L), the difference was statistically significant with p-value <0.001. In the multiple regression analysis, sclerostin level remained one of the statistically significant predictors (p-value <0.05) for CIMT. **Conclusion:** We can conclude that serum sclerostin is independently associated with carotid atherosclerosis (CIMT, plaques) in hemodialysis patients.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) accounting for more than 50% of causes of death**.**[1]

CKD patients have unique, non-traditional or '**novel**' risk factors, in addition to traditional risk factors, such as disordered mineral, abnormal bone turnover, vascular calcification (VC), all of which are collectively form an entity called chronic kidney disease-mineral bone disorder **(CKD-MBD).**[2]

Many studies had explored the role of novel circulating pathogenic factors in the CKD-MBD, such as FGF23, Klotho, and wingless/integrated-1 (Wnt) inhibitors, including their involvement in cardiovascular disorders in CKD. Any kidney injury, in an attempt to repair, leads to reactivation of normally silent signals involved in nephrogenesis; one of the most important is the Wnt pathway which proved to have a direct effect on the vasculature, the myocardium, and the skeleton.[3] Activation of the canonical Wnt pathway is associated with an increase in expression of Wnt inhibitors that control its activation by a negative feedback mechanism.[4]

Sclerostin, a soluble antagonist of the canonical Wnt/β-catenin signaling pathway in osteoblasts, act via binding to LRP5/6. It is a secreted glycoprotein of SOST gene first known in 2001.[5] The newly embedded osteocytes are the main cells producing and secreting it and to a lesser extent other cell types, including osteoblasts, osteoclast precursors, renal and vascular cells.[6]

On the bone, the main action of sclerostin is decreasing osteogenesis via inhibiting osteoblast proliferation and differentiation and promoting osteoblast apoptosis.[7] In addition, sclerostin can stimulate bone resorption, via increasing osteocytic expression and secretion of RANKL, this lead to increased osteoclast production and activation.[8] Thus, the neutralizing anti-sclerostin antibodies (Romosozumab) can uniquely achieve dual action (both anabolic and anti-resorptive actions) in the treatment of osteoporosis.[9] On vasculature, there is mounting evidence about the extra-skeletal expression of sclerostin especially the cardiovascular system, where it also antagonizes Wnt signaling.[10]

Nowadays, it is believed that vascular calcification is an active process resulting from the osteoblastic transition of VSMCs via a Wnt-dependent mechanism, which in turn activate osteocyte-specific proteins such as sclerostin and FGF23.[11] Therefore, we can speculate that Wnt signaling inhibitors could prevent osteoblast maturation and consequently the progression of cardiovascular calcification.[10]

Many studies had demonstrated that the serum sclerostin level increases in CKD patients especially ESRD. Whether this is due to decreased clearance or increased skeletal or extra skeletal production is unclear.[12] Atherosclerosis is one of two main forms of vascular calcification affecting ESRD patients.[13] Studies demonstrated that sclerostin was found in atherosclerotic plaques and that osteoblastic transition of VSMCs resulting in increased expression of sclerostin in vascular calcified tissues as a negative feedback to prevent the further calcification.

However till now, as shown in meta-analysis made by **Kanbay et al. 2016,** the results of several cross-sectional studies which investigated the association of serum sclerostin levels with vascular calcification were conflicting, some studies showing a positive association[14], others showed negative association[15,16], and some show no association.[17,18]

Due to these contradicting data, the aim of our study is to investigate the association of circulating concentrations of sclerostin with carotid artery atherosclerosis in hemodialysis patients.

## PATIENTS & METHODS

### A. Study population

This is a case-control study that included one hundred and fifty patients on regular hemodialysis in the University and General hospitals, Fayoum government, in February 2017. Fifty sex- and age-matched healthy controls were included. The study was reviewed and approved by the local ethics committee of Fayoum University. Informed consents were obtained from all study participants.

Inclusion criteria include patients' age between 18y – 70y.old and patients receiving long-term maintenance hemodialysis (MHD) with a dialysis frequency of three times/ week, 4 hours/ session for ≥ 1 year. Patients with primary hyperparathyroidism, signs of liver cell failure (LCF), malignancy or signs of active infection were excluded from our study.

**B. Methods**

All patients were subjected to the following:

**1.** Full history taking including the cause of ESRD, hemodialysis vintage, smoking, history of hypertension, diabetes, cardiovascular events, use of antihypertensive treatment, statins, antiplatelet, alfacalcidol, and Calcium-based phosphate binders.

**2.** Thorough clinical examination including blood pressure measurement and BMI calculation.

**3.** Blood samples were collected at the beginning of the dialysis session and then stored at -80ºC until further analysis.

**4.** Laboratory tests were done including serum creatinine, serum urea, total serum calcium ($Ca^{2+}$), serum phosphorus, lipid profile, hemoglobin (Hb), C-reactive protein (CRP), alkaline phosphatase (ALP), and serum albumin.

**5.** Measurement of serum sclerostin using a commercially available ELISA (Biomedica, EIAab®, Wuhan, China, 2017).

**6.** Imaging of carotid artery for measurement of intima-media thickness (CIMT) and detection of carotid plaques by carotid duplex using LOGIQ S8 XDclear ultrasound machine (GE Healthcare Inc., USA) with 5-10 MHZ linear probe.

**C. Statistical analysis**

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using statistical package for the social sciences software (SPSS software 17; SPSS Inc., Chicago, USA). For quantitative parametric data in-depended student t-Test used to compare measures of two independent groups of quantitative data. One-way ANOVA test in comparing more than two independent groups of quantitative data with Bonferroni post-hoc to test significance between each two groups. For qualitative data, bivariate Pearson correlation test to test the association between variables. Chi-square test was used to compare two

or more than two qualitative groups. Multiple linear regressions to test the association between quantitative dependent and independent variables and detection of risk factors. P-value < 0.05 was considered the cut-off value for significance.

# Results

## A. Demographic and clinical characteristics of study groups

Our study is a case-control study which included 150 patients on regular hemodialysis and 50 healthy persons as a control group. As shown in the table (1), there is no statistically significant difference (p-value>0.05) between cases and controls as regard age and sex distribution which indicated proper matching between groups.

Table 1 illustrates that a statistically significant difference (p-value<0.001) between cases and controls regarding CIMT with high mean among cases. Regarding sclerostin levels, there is a statistically significant difference (p-value <0.001) between cases (83.5±27.1) and controls (26.3±5.8) with high mean among cases. Collectively, these data could suggest that sclerostin levels are related to CIMT in hemodialysis patients.

Table (2) demonstrated that the most frequent cause of ESRD among cases was hypertension (HTN) (32.7%) followed by obstruction (16%), then diabetes mellitus (DM) (13.3%) and the lowest frequent case was polycystic kidney disease (PKD) (6%).



## B. Association of sclerostin levels and CIMT with Baseline Demographic and Clinical Characteristics of the Study Population

Table (3) illustrates that the mean sclerostin level is higher in males than females in all study participants but this difference is not statistically significant (p-value >0.05.)

Sclerostin levels are significantly higher (p-value=0.002) in patients developed ESRD because of HTN, DM, and PKD. Similarly, the sclerostin levels are significantly higher (p-value<0.05) in patients with HCV and DM than those without. Also, sclerostin is significantly higher in dialysis patients treated with antiplatelets. On the other hand, there is no statistically significant difference (p-value >0.05) in sclerostin levels among patients with hypertension, CVD, and smokers.

As regard CIMT, there is no statistically significant difference (p-value >0.05) in CIMT between different sex. CIMT is significantly higher (p-value <0.05) in patients with a history of HCV, HTN, DM, CVD, and smokers. Also, CIMT is significantly higher (p-value=0.001) in ESRD patients because of DM, HTN, and PKD. CIMT is found to be also higher in patients treated with statins, antiplatelet, and ACEI.

Table (4) illustrates a significant positive correlation (r= 0.32, p-value <0.001) between age and sclerostin level indicating that an increase in age is associated with an increase in sclerostin level. A positive correlation was found between sclerostin and BMI, systolic and diastolic blood pressures.

A negative correlation between sclerostin level and each of patients' phosphorus, ALP, albumin, HDL, CRP, TC, and LDL levels, indicating that the increase in these parameters was associated with a decrease in sclerostin levels among cases. On the other hand, no correlation could be found between sclerostin levels and dialysis vintage.

Importantly, a significant positive correlation between sclerostin and CIMT (r=0.7) and between sclerostin and plaques size; (width, r=0.51) and (length, r=0.53); which indicate that the increase in CIMT and plaques size of patients was associated with an increase in sclerostin levels.

Next, we studied correlations of CIMT. A significant positive correlation was found between CIMT and each of patients' age, BMI, SBP, and DBP. Similarly, there is a positive correlation between CIMT and each of patients' CRP, TG, TC, and LDL levels. Differently, CIMT negatively correlates with each of patients' ALP, albumin, and HDL levels. Like sclerostin, there is no correlation between CIMT and dialysis vintage.

**C. Sclerostin levels are higher in patients with plaque formation**

To prove the relation between sclerostin and CIMT and plaques, we compared sclerostin levels in different CIMT. Table 5 illustrates that sclerostin significantly increased with increased CIMT and further increased with plaque formation.

**D. Linear regression analysis to determine risk factors**

The linear logistic regression model analysis was conducted to explore the explanatory power of different risk factors on sclerostin levels among cases, it illustrated that there were statistical significance predictors with p-value <0.05 to ALP, CIMT, calcium and phosphorus level. Prediction power of sclerostin level is 84% when applied this model of regression.

Similarly, the linear logistic regression model analysis was conducted to explore the explanatory power of different risk factors on CIMT among cases. This illustrates that there were statistical significance predictors with p-value <0.05 to CRP, age, LDL, HDL, calcium level, DM, and sclerostin level. Prediction power of CIMT level is 90% when applied this model of regression.

## Discussion

The horrible prevalence of cardiovascular morbidity and mortality among CKD patients especially ESRD patients raised the suspicion for the presence of additional, unique risk factors for CKD.

Advances during the last decade pointed to the role of disturbed Wnt/β-catenin signaling pathway and its inhibitors, notably sclerostin, in the pathogenesis of CKD-MBD, either through their involvement in bone turnover disorders or in vascular calcification.[19]

On vasculature, many studies demonstrated that vascular calcification is a process resembling osteogenesis that involves the phenotypic transformation of VSMC into bone-forming osteoblast-like cells; this is regulated by Wnt pathway and its inhibitors including sclerostin.[20,21]

One of the two main forms of vascular calcification complicating CKD is atherosclerosis.[22] Subclinical atherosclerosis can be detected by increased carotid intima-media thickness (CIMT) using carotid ultrasound.[23,24]

All stages of the atherosclerosis process and its complications are mostly associated with upregulation of Wnt signaling with an increased production of its inhibitors like sclerostin, as a defensive mechanism.[25]

Studies had investigated the association between sclerostin level and CIMT in different types of study populations with contradictory results.[26] Understanding the nature of this association is of particular importance because anti-sclerostin antibodies are currently being developed as a new treatment of osteoporosis.[27] Furthermore, it might help to broadly use sclerostin as a simple, easy, fast biomarker for prediction of bone and vascular diseases in CKD (CKD-MBD).

The current study had investigated the association between serum sclerostin levels, carotid artery atherosclerosis in hemodialysis patients. There was a significant positive correlation (p-value <0.001) between sclerostin level and each of CIMT (r = 0.56) and CCA plaques size (r = 0.53).

The sclerostin level was significantly higher (p-value <0.001) in patients with increased CIMT (77.6±17.8) than with normal CIMT (70.9±9.6) and the highest mean was among patients with plaque formation (109.3 ± 35.1). There is mounting evidence that the Wnt signaling pathway and its components are upregulated during all processes of atherosclerosis.[25] Sclerostin may act by inhibition of the canonical Wnt pathway consequently, may dampen the atherogenesis.[28] Also, sclerostin is an important inhibitor of alkaline phosphatase (ALP) activity, which inactivates the potent calcification inhibitor, the inorganic pyrophosphate.[29]

Therefore, we can speculate that sclerostin may act as a vasculoprotective agent against atherosclerosis and vascular calcification and that the high sclerostin level may be a defensive mechanism or a negative feedback that tries to attenuate the upregulated Wnt pathway during atherogenesis.

In this context, it is worth to be mentioned that cross-sectional studies investigating the association between sclerostin and CIMT, yielded conflicting results with some studies reported positive association like our study.[30] Others depicted negative association[26,31] and no association.[17, 18]

This may be explained by different demographic and clinical characteristics of the study populations and different ELISA techniques (TECOmedical and Biomedica) used in the measurement of serum sclerostin level in the different studies.[32]

Also, there was a negative correlation between sclerostin level and ALP (r = -0.79) with a statistically significant difference with p-value <0.001. This agrees with the other studies.[12,19] This

support the notion of that high sclerostin level has a role in either development or aggravation of ABD in CKD and this via inhibition of Wnt pathway and worsening of PTH resistance in CKD.[33]

The explanatory power of different risk factors on CIMT among cases was explored by the linear logistic regression model analysis which illustrated that there were statistical significance predictors with p-value <0.05 to sclerostin level, DM, age, LDL, HDL, CRP, and calcium level.

Finally, when the linear logistic regression model analysis conducted to explore the explanatory power of different risk factors on sclerostin levels among cases, it illustrated that there were statistical significance predictors with p-value <0.05 to CIMT, ALP, calcium and phosphorus level.

In conclusion, we can conclude that serum sclerostin is independently associated with carotid atherosclerosis (CIMT, plaques) in hemodialysis patients and that sclerostin could represent a promising biomarker for bone and vascular affection of CKD-BMD.

It became an essential task to clarify the precise role of sclerostin in the pathogenesis of atherosclerosis, and in vascular calcification in general.

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**Table (1): Demographic characteristics of study groups**

| Parameter | | Cases | Controls | p-value |
|---|---|---|---|---|
| Age | | 47.3±14.5 | 44.2±8.7 | 0.2 |
| Sex | Males | 83 (55.3%) | 24 (48%) | 0.4 |
| | Females | 67 (44.7%) | 26 (52%) | |
| Sclerostin | | 83.5±27.1 | 26.3±5.8 | 0.001 |
| **CIMT measurement (mm)** | | | | |
| CIMT (mm) Rt | | 0.93±0.22 | 0.66±0.07 | **<0.001** |
| CIMT (mm) Lt | | 0.88±0.20 | 0.65±0.07 | **<0.001** |
| CIMT (mm) mean | | 0.90±0.21 | 0.65±0.07 | **<0.001** |
| **Frequency of normal CIMT** | | | | |
| Normal CIMT | | 67 (44.7%) | 47 (94%) | **<0.001** |
| Increased CIMT without plaques | | 41 (27.3%) | 3 (6%) | **<0.001** |
| Plaque formation | | 42 (28%) | 0 (0%) | **<0.001** |

*Increased CIMT mean **≥ 9**mm, while plaques defined as a focal wall thickening > **50%** (or **0.5** mm) of the surrounding IMT, or it's CIMT > **1.5** mm.

## Table (2): Baseline demographic and clinical characteristics of patients

| Parameter | Mean | SD | Min | Max |
|---|---|---|---|---|
| Dialysis vintage (years) | 4.6 | 3.4 | 1 | 18 |
| BMI | 25.9 | 4.1 | 18 | 34 |
| Systolic BP | 138.2 | 11.5 | 110 | 160 |
| Diastolic BP | 85 | 7.8 | 70 | 100 |
| **Investigations** | | | | |
| Serum creatinine | 6.9 | 1.5 | 4.2 | 10.9 |
| Serum urea | 144.8 | 31.2 | 88 | 301 |
| Corrected $Ca^{+2}$ | 8.2 | 1.2 | 5 | 11.3 |
| $Po_4$ | 5.1 | 1.1 | 2.1 | 9 |
| ALP | 174.5 | 51.6 | 65 | 273 |
| HB | 10.7 | 1.7 | 5.7 | 16.4 |
| Albumin | 4.1 | 0.39 | 3.5 | 5.6 |
| CRP | 13.7 | 5.9 | 6 | 29 |
| TG | 187.8 | 61.8 | 84 | 451 |
| TC | 180.2 | 26.4 | 128 | 295 |
| LDL | 105.1 | 27.3 | 62.2 | 213 |
| HDL | 38.2 | 8.5 | 12 | 53 |
| **Frequency of different causes of ESRD among cases** | | | | |
| Hypertension (**HTN**) | **49** | 32.7% | N/A | N/A |
| Obstructive | **24** | 16% | N/A | N/A |
| Diabetes mellitus (**DM**) | **20** | 13.3% | N/A | N/A |
| Unknown | 13 | 8.7% | N/A | N/A |
| Drug-induced | 12 | 8% | N/A | N/A |
| Chronic Glomerulonephritis (**GN**) | 12 | 8% | N/A | N/A |
| Chronic Pyelonephritis | 11 | 7.3% | N/A | N/A |
| Polycystic kidney disease (**PKD**) | **9** | 6% | N/A | N/A |
| **Frequency of medical history among cases** | | | | |
| HTN | 99 | 66% | N/A | N/A |
| HCV | 55 | 36.7% | N/A | N/A |
| Smoking | 48 | 32% | N/A | N/A |
| CVD | 17 | 11.3% | N/A | N/A |
| DM | 20 | 13.3% | N/A | N/A |
| **Frequency of medications among cases** | | | | |
| Calcium-based phosphate binders | 122 | 81.3% | N/A | N/A |
| Alfacalcidol | 79 | 52.7% | N/A | N/A |
| Antiplatelets | 17 | 11.3% | N/A | N/A |
| Statins | 5 | 3.3% | N/A | N/A |
| **Anti-hypertensive drugs** | | | | |
| No | 54 | 36% | N/A | N/A |
| Mixed | 51 | 34% | N/A | N/A |
| Ca Channel | 29 | 19.3% | N/A | N/A |
| BB | 15 | 10% | N/A | N/A |
| ACEI | 1 | 0.7% | N/A | N/A |

**Table (3): Sclerostin levels and CIMT among study groups**

| Parameter | | Sclerostin | | CIMT | |
|---|---|---|---|---|---|
| | | mean±SD | p-value | mean±SD | p-value |
| **Gender** | | | | | |
| Male (all) | | 70.8±34.9 | 0.5 | 0.85±0.21 | 0.5 |
| Female (all) | | 67.4±33.6 | | 0.83±0.21 | |
| Male (cases) | | 83.4±29.1 | 0.9 | 0.91±0.21 | 0.8 |
| Female (cases) | | 83.6±24.5 | | 0.89±0.21 | |
| **Causes of ESRD** | | | | | |
| Hypertension | | **83.6±27.6** | **0.002** | **0.95**±0.17 | **0.001** |
| DM | | **107.1±29.9** | | **1.12**±0.22 | |
| Obstructive | | 82.2±35.9 | | 0.86±0.23 | |
| Drug-induced | | 78.8±22.9 | | 0.85±0.23 | |
| Chronic GN | | 75.8±7.8 | | 0.79±0.10 | |
| Chronic pyelonephritis | | 72.9±8.6 | | 0.74±0.09 | |
| PKD | | **84.7±17.3** | | **0.89**±0.09 | |
| Unknown | | 68.9±4.5 | | 0.77±0.12 | |
| **Medical History** | | | | | |
| HCV | Yes | 79.7±24.7 | **0.02** | 0.86±0.18 | **<0.001** |
| | No | **90.1±29.7** | | **0.98**±0.22 | |
| HTN | Yes | 77.8±20.7 | 0.06 | 0.82±0.22 | **<0.001** |
| | No | 86.4±29.5 | | 0.95±0.18 | |
| DM | Yes | 80.4±24.8 | **<0.001** | 0.87±0.17 | **<0.001** |
| | No | **109.9±31.9** | | **1.2**±0.21 | |
| CVD | Yes | 83.4±27.9 | 0.9 | 0.89±0.21 | **0.01** |
| | No | 84.1±20.1 | | 1.02±0.17 | |
| Smoking | Yes | 81.1±25.4 | 0.1 | 0.88±0.20 | **0.02** |
| | No | 88.6±29.9 | | **0.96**±0.21 | |
| **Medications** | | | | | |
| Statin | Yes | 83.1±27.3 | 0.4 | 0.89±0.21 | **0.02** |
| | No | 94.3±17.2 | | 1.1±0.11 | |
| Aspirin | Yes | 81.5±25.2 | **0.01** | 0.89±0.20 | **0.003** |
| | No | **99.3±35.9** | | 1.04±0.21 | |
| Alfacalcidol | Yes | 81.5±26.6 | 0.3 | 0.88±0.21 | 0.3 |
| | No | 85.7±27.6 | | 0.92±0.21 | |
| Ca based binders | Yes | 82.6±27.1 | 0.4 | 0.95±0.18 | 0.2 |
| | No | 82.6±27.1 | | 0.89±0.21 | |
| **Antihypertensives** | | | | | |
| NO | | 77.7±20.2 | 0.3 | 0.83±0.22 | **0.003** |
| BB | | 87.1±25 | | 0.98±0.20 | |
| Ca Channel | | 83.9±29.1 | | 0.92±0.18 | |
| ACEI | | 214.1±0 | | 1.3±0 | |
| Mixed | | 85.8±26.7 | | 0.94±0.18 | |

**Table (4): Correlations of CIMT and Sclerostin with different study parameters**

| Parameter | CIMT | | Sclerostin | |
|---|---|---|---|---|
| | r | p | r | p |
| **Age** | **0.65** | **<0.001** | **0.32** | **<0.001** |
| BMI | 0.34 | <0.001 | 0.22 | 0.008 |
| Systolic BP | 0.43 | <0.001 | 0.27 | 0.001 |
| Diastolic BP | 0.41 | <0.001 | **0.30** | **<0.001** |
| Triglycerides | 0.28 | 0.001 | 0.09 | 0.2 |
| **Total cholesterol** | **0.66** | **<0.001** | **0.34** | **<0.001** |
| **LDL** | **0.67** | **<0.001** | **0.38** | **<0.001** |
| **HDL** | **-0.53** | **<0.001** | **-0.32** | **<0.001** |
| Hb | -0.08 | 0.3 | -0.07 | 0.4 |
| Albumin | -0.28 | <0.001 | **-0.13** | **0.01** |
| Calcium | 0.1 | 0.2 | -0.08 | 0.3 |
| Phosphate | -0.06 | 0.5 | **-0.27** | **0.001** |
| **CRP** | **0.80** | **<0.001** | **0.46** | **<0.001** |
| **ALP** | **-0.48** | **<0.001** | **-0.79** | **<0.001** |
| Creatinine | 0.18 | 0.03 | 0.04 | 0.7 |
| Urea | 0.09 | 0.2 | 0.04 | 0.6 |
| Dialysis vintage (years) | -0.09 | 0.7 | -0.02 | 0.8 |
| **Sclerostin** | **0.7** | **<0.001** | N/A | N/A |
| **CIMT** | N/A | N/A | **0.7** | **<0.001** |
| Plaque width (mm) | N/A | N/A | 0.51 | <0.001 |
| Plaque length (mm) | N/A | N/A | 0.53 | <0.001 |

**Table (5): Comparison of mean sclerostin level in different CIMT among cases**

| CIMT | Sclerostin level | |
|---|---|---|
| | **Mean±SD** | **p-value** |
| Normal | **70.9±9.6** | **<0.001** |
| Increased CIMT without plaque. | **77.6±17.8** | **<0.001** |
| Plaque formation | **109.3±35.1** | **<0.001** |

**Table (6): Multiple linear regression analysis to determine the risk factors of increase in sclerostin levels and CIMT among cases**

| Variables | B | SE | Sig. | CI |
|---|---|---|---|---|
| **Sclerostin** | | | | |
| **Constant** | 161.7 | 13.6 | <0.001 | 134.8-188.6 |
| **ALP** | -0.34 | 0.03 | <0.001 | -0.39-(-0.29) |
| **CIMT** | 32.7 | 6.8 | <0.001 | 19.2-46.2 |
| **Ca** | -3.72 | 1.1 | 0.001 | -5.8-(-1.6) |
| **$Po_4$** | -3.38 | 1.2 | 0.005 | -5.7-(-1.05) |
| **CIMT** | | | | |
| **Constant** | 0.35 | 0.09 | <0.001 | 0.16-0.53 |
| **CRP** | 0.02 | 0.002 | <0.001 | 0.01-0.02 |
| **Age** | 0.003 | 0.001 | <0.001 | 0.001-0.004 |
| **LDL** | 0.001 | 0.00 | <0.001 | 0.001-0.002 |
| **DM** | 0.10 | 0.02 | <0.001 | 0.049-0.16 |
| **Sclerostin level** | 0.001 | 0.00 | 0.001 | 0.00-0.002 |
| **HDL** | -0.003 | 0.001 | 0.004 | -0.005-(-0.001) |
| **Ca** | 0.02 | 0.007 | 0.04 | 0.00-0.027 |