The relationship between sclerostin and carotid artery atherosclerosis in patients with stages 3-5 chronic kidney disease

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Abstract

Background: Sclerotin is an antagonist of the Wnt-β-catenin pathway, may play an important role in the pathophysiology of artery atherosclerosis. Previously, we reported that sclerostin was closely related to carotid atherosclerosis and the long-term outcomes of hemodialysis patients. Here, we aimed to investigate the associations of sclerostin with renal function and carotid artery atherosclerosis in non-dialysis patients with chronic kidney disease in stages 3–5 (CKD 3–5ND). Methods: A total of 140 patients with CKD 3–5ND were enrolled in this cross-sectional study. The Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) was used to estimate glomerular filtration rate (eGFR). Carotid artery atherosclerotic plaques were identified by B-mode Doppler ultrasound. Blood samples were collected to assess serum sclerostin. Unconditional logistic regression analysis was used to assess risk factors for carotid atherosclerotic plaques. Results: The median eGFR and serum sclerostin were 24.9 mL/min/1.73m 2 (interquartile range: 10.0 to 40.3 mL/min/1.73m 2) and 46.76 pmol/L (interquartile range: 30.18 to 67.56 pmol/L) , respectively. Carotid atherosclerotic plaques were detected in 104 subjects (74.3%). There was a negative association between sclerostin and eGFR (r = -0.214, p = 0.011). Unconditional logistic regression revealed that sclerostin was an independent factor that was significantly related to the presence of carotid plaques, with odds ratio (OR) of 1.026 (1.003, 1.051). Conclusions: Patients with CKD 3–5ND showed a gradual increase in serum sclerostin with declining renal function, and sclerostin is an independent correlate for carotid atherosclerosis.

Background

The prevalence of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) is much higher than that in the general population [1, 2]. Numerous findings have suggested that the Wnt/β-catenin signaling pathway plays an important role in the pathophysiology of atherosclerosis [3-5]. The Wnt-β-catenin signaling pathway is an important player in bone remodeling, and is involved in osteoblast proliferation, differentiation and bone formation [6, 7]. Dysregulation of the Wnt-β-catenin pathway also plays a crucial role in chronic kidney disease–mineral bone disorder (CKD-MBD) [6]. Sclerotin is a product of the SOST gene. This glycoprotein is an antagonist of the Wnt-β-catenin pathway and is predominantly secreted by osteoblasts, and plays a powerful anti-anabolic role in the formation of bone [6]. In mice, inactivating mutations in the SOST gene lead to increased bone mass [8], while activating mutations result in bone loss [9].In addition, monoclonal antibodies raised against sclerostin have been used in postmenopausal women with osteoporosis, resulting in a dose-dependent increase in bone mineral density [10].

In a previous study, Pelletier et al. found that the levels of serum sclerostin were significantly higher in CKD patients than in the general population, and started to increase during CKD stage 3 [11]. However, the specific mechanisms underlying the elevation of sclerostin in CKD remain poorly understood, but are thought to be related to renal retention [12] and/or enhanced production by osteocytes [13]. The exact role of increased sclerostin in the induction or prevention of anomalies in bone turnover in

CKD patients, still remains poorly understood.

Sclerostin has been detected on the surface of mineralized osteoblast-like cells *in vitro* and in the calcified aortic valve tissue of patients undergoing hemodialysis (HD) [14, 15]. More recently, Leto et al. detected sclerostin in carotid atherosclerotic plaques by immunohistochemistry [16]. Clinical studies have also observed a correlation between serum sclerostin levels and atherosclerosis in obese and diabetic patients [17, 18]. Our previous research has also shown that serum sclerostin is closely related to atherosclerosis and the long-term survival of HD patients [19]. Consequently, we speculated that sclerostin also plays an important role in the pathophysiology of atherosclerosis. Few existing study has attempted to investigate the correlation between serum sclerostin level and atherosclerosis in non-dialysis patients with chronic kidney disease (CKD-ND) [20]; interestingly, the conclusions from this work were not consistent with those from studies investigating patients undergoing HD [19, 21]. Therefore, the present study aimed to analyze the relationship between sclerostin and atherosclerosis in non-dialysis patients with chronic kidney disease in stages 3–5 (CKD 3–5ND).

Methods

Study population

A total of 140 patients aged ≥18 years with CKD 3–5ND were enrolled as study subjects between February 2015 and October 2016. Patients under systemic immunosuppressive medication and those with active cancer disease, malignant hematological disorders, acute renal failure, active liver disease, fractures, and/or acute and chronic infections were excluded from the study.

A detailed medical history, including age, gender, height, weight and the causes of CKD (chronic glomerulonephritis, hypertensive renal disease, diabetic nephropathy, chronic interstitial nephritis, polycystic kidney disease, autoimmune diseases or other diseases) were collected. We also acquired information relating to medical history, smoking (Patients who had quit smoking for more than 5 years were classified as non-smokers), diabetes mellitus (DM), and hypertension (including primary and renal hypertension).

The study was approved by the local ethics committee of Beijing Hospital (Number: 2014BJYYEC-058-01), and written informed consent was obtained from all patients.

Kidney Function Measurement

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI), as shown below:

$$eGFR = 175 \times Scr^{-1.154} \times age^{-0.203} (\times 0.742, \text{if female}).$$

eGFR data were then used to classify patients into different CKD stage groupings, as follows: stage 3 (eGFR: 30–60 mL/min/1.73 m^2), stage 4 (eGFR: 15–30 mL/min/1.73 m^2) and stage 5 (eGFR: <15

mL/min/1.73 m^2).

Biochemical parameters

Venous blood samples were taken in a fasting state, and serum creatinine levels were measured by the enzymatic isotope dilution mass spectrometry (IDMS) traceable standardized method (Roche Cobas C501 Biochemical Analyzer, Roche Diagnostics, Mannheim, Germany) in our biochemical laboratory. The serum levels of uric acid, total serum calcium, phosphate, albumin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alkaline phosphatasev(ALP), high-sensitivity C-reactive protein (hs-CRP), intact parathyroid hormone (iPTH) and hemoglobin were determined according to the standard laboratory methods at the hospital's central laboratory. All serum samples were then stored at -80°C until to October 2016, an enzyme-linked immunosorbent assay (ELISA) kit (Biomedica, Austria) was used to determine the serum levels of sclerostin. Simultaneously, 18 patients with normal renal function (11 males, 7 females, mean age 59.9 years) were recruited as the control group, with a median sclerostin level of 36.31 (26.29, 43.60) pmol/L.

B-mode and Doppler ultrasound of the common carotid arteries

B-mode and Doppler ultrasound of the common carotid arteries was performed at baseline. An atherosclerotic plaque was defined as a focal structure that encroached into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) value, or that has a thickness >1.5 mm, as measured from the media-adventitia interface to the intima-lumen interface [22]. The sonographer looked for the presence of plaques by scanning the common carotid artery, the bifurcation of the carotid artery, the proximal internal carotid artery and the external carotid artery segment, in both a longitudinal and cross-sectional manner [23]. The carotid arteries were detected bilaterally using color Doppler ultrasound at a frequency of 5–10 MHz (model IU-22; Philips, Netherlands) by an experienced sonographer, with each measurement repeated twice.

Statistical analyses

Statistical analyses were performed with SPSS 20.0 software (version 20.0, IBM Corp., Armonk, NY, USA). The normality of raw data was determined by the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), and non-normally distributed continuous variables as median with 25^{th} and 75^{th} percentiles. Differences between groups were compared using the Student's t test or the Mann-Whitney U test, depending upon whether the data were normally distributed or not. Categorical data were expressed as percentages and assessed using the chi-square test. Spearman's method was used to investigate the correlation between sclerostin and other parameters. Finally, risk factors for carotid atherosclerotic plaques were assessed by unconditional logistic regression. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline patient characteristics

The demographic and clinical characteristics of the study cohort are shown in Table 1. A total of 140 subjects (age range, 25–81 years) were enrolled, including 60 patients with DM (44.3%). Of these patients, the causes of CKD were chronic glomerulonephritis (n = 41, 29.3%), hypertensive renal disease (n = 39, 27.9%), diabetic nephropathy (n = 33, 23.6%), chronic interstitial nephritis (n = 15, 10.7%), polycystic kidney disease (n = 3, 2.1%), autoimmune diseases (n = 2, 1.4%) and other diseases (n = 7, 5.0%). There were 58, 36 and 46 patients in CKD stages 3 (41.4%), 4 (25.7%) and 5 (32.9%), respectively.

The median eGFR was 24.9 mL/min/1.73m^2, and the median serum sclerostin concentration was 46.76 pmol/L. Carotid atherosclerotic plaques were detected in 104 subjects (74.3%). Males had significantly higher serum sclerostin levels compared with females (57.26 *vs.* 43.05 pmol/L; median, $p < 0.001$). While patients with a history of smoking (59.08 *vs*. 45.93 pmol/L; median, $p = 0.063$) and hypertension (47.75 *vs.* 34.41 pmol/L; median, $p = 0.056$) tended to have higher sclerostin levels compared with those without. Sclerostin levels were comparable between patients with and without DM (47.28 *vs*. 45.75 pmol/L; median, $p = 0.273$).

Relationships between serum sclerostin and both renal function and bone and mineral metabolism markers

With the deterioration of renal function, levels of serum sclerostin gradually increased. Spearman correlation analysis showed that serum sclerostin was negatively correlated with eGFR (r = -0.214, $P = 0.011$), and the sclerostin level in patients with CKD stage 5 was significantly higher than that in patients with CKD stage 3 (42.53 *vs*. 52.64 ng/mL, median, $p = 0.048$), but the levels were comparable in patients with CKD stage 3 and 4 (42.53 *vs*. 44.11 ng/mL, $p = 0.741$) and in patients with CKD stage 4 and 5 (44.11 *vs*. 52.64 ng/mL, $p = 0.115$), as shown in Figure 1. Spearman correlation analysis showed that serum sclerostin was negatively correlated with calcium (r = -0.225, $P = 0.007$), but positively correlated with phosphorus (r = 0.185, $P = 0.028$). There were no significant correlations between serum sclerostin and iPTH, hs-CRP or alkaline phosphatase.

Differences between the characteristics of the high and low sclerostin groups

The subjects (n = 140) were divided into two groups according to the median sclerostin levels (46.76pmol/L, “high” and “low” groups), as in previous studies [19]. The subjects in the high group showed a higher proportion of male patients ($p = 0.042$) and higher levels of serum phosphate ($p = 0.002$), and lower levels of eGFR ($p = 0.020$), serum total calcium ($p = 0.007$), hemoglobin ($p = 0.008$) and ALP ($p = 0.034$). (Table 1).

Comparisons between patients with and without atherosclerotic plaques

Subjects were divided into two groups according to whether they had carotid atherosclerotic plaques or not: a plaque group (n = 104) and a non-plaque group (n = 36). The plaque group had higher levels of serum sclerostin ($P = 0.013$), as shown in Figure 2. Moreover, the plaque group was significantly older ($P < 0.001$) and had a higher prevalence of hypertension ($P = 0.007$) and DM ($P < 0.001$), compared with the non-plaque group. (Table 2).

Factors related to carotid atherosclerotic plaques

Unconditional logistic regression analysis was used to analyze the related factors for carotid atherosclerotic plaques, and age, body mass index (BMI), DM, hypertension, eGFR and sclerostin ($p < 0.05$) were used as independent variables, and the presence of carotid atherosclerotic plaques was used as the dependent variable. This analysis showed that age, BMI, DM and sclerostin were independent factors that were significantly related to the presence of carotid plaques, with odds ratios (ORs) of 1.136 (1.082, 1.192), 1.170 (1.000, 1.369), 3.372 (1.020, 11.142) and 1.026 (1.003,1.051), respectively (Table 3).

Discussion

This study found a strong negative relationship between serum sclerostin levels and renal function, and identified independent associations between serum sclerostin levels and carotid plaques in patients with CKD 3–5ND. While the increase in sclerostin levels with declining renal function has been well described in previous studies [11, 24], the specific mechanisms underlying elevated serum sclerostin levels in CKD patients have not yet been fully elucidated. In a previous study, Cejka et al. observed that urinary sclerostin excretion increased with decreasing eGFR, and noted that higher sclerostin levels in CKD patients were not related to a decline in renal function [25]. In a recent study, Graciolli et al. reported that the percentage of sclerostin-positive osteocytes in CKD patients was significantly higher when compared with a control group (38% in a group of patients with stage 2 – 3 CKD, 26% in patients with stage 4 CKD and 5.3% in the control group), and noted that the higher sclerostin levels in CKD patients may be partly derived from increased production by osteocytes [13]. In another study, Brandenburg et al. detected the expression of sclerostin by immunohistochemistry in calcified aortic valves in HD patients, they also found that serum sclerostin levels were closely associated with calcifying vasculature [15]. These authors went on to speculate that sclerostin may partly originate from an extra-skeletal source [15].

Atherosclerotic plaque formation is a complex process that involves vascular calcification, inflammation, endothelial dysfunction, and the proliferation and migration of vascular smooth muscle cells (VSMCs) [3]. Numerous studies have demonstrated that the Wnt-β-catenin pathway plays an important role in the pathophysiological process of atherosclerosis, and in the regulation of endothelial inflammation [26], mesenchymal stem cell differentiation [27, 28], and the proliferation, migration and survival of VSMCs [4]. The Wnt protein is also known to promote the adhesion of monocytes to endothelial cells [29]. Other

research showed that missense mutations in the low-density lipoprotein (LDL) receptor-related proteins 6 (LRP6, a receptor of the Wnt ligand) were associated with the increased incidence of early-onset coronary artery disease, hypertension, high-serum LDL and DM [30]. Sclerotin is a soluble antagonist of the Wnt-β-catenin pathway, and interrupts this pathway by interfering with the extracellular binding of the Wnt ligand to the transmembrane receptor complex [6]. Leto et al. investigated sclerostin expression in atherosclerotic plaques, and found that levels of sclerostin were significantly increased in the media compared with the intima, and in vascular smooth muscle cells compared with infiltrating macrophages [16]. In another study, Krishna et al. observed that sclerostin may play a protective role in maintaining aortic homeostasis by inhibiting inflammation and degradation of the extracellular matrix [31]. The same authors also found that both the transgenic introduction of human sclerostin, and the administration of recombinant mouse sclerostin into apolipoprotein E-deficient mice, inhibited angiotensin II-induced aneurysm formation and atherosclerosis [31]. In the present study, we also found that sclerostin was independently associated with atherosclerotic plaques, and our previous publication reported a similar conclusion for HD patients [19]. Collectively, these findings suggest that sclerostin may play an important role in the process of atherosclerosis. We hypothesize that sclerostin may inhibit the process of atherosclerosis by inhibiting the Wnt pathway, and that the production of sclerostin by atherosclerotic plaques may act as a negative feedback protective mechanism against the development of atherosclerotic plaques. Consequently, the more severe the atherosclerosis, the more sclerostin is secreted. Further studies are now required to determine the exact role of sclerostin in atherosclerosis, and the precise involvement of the Wnt-β-catenin axis in this process.

iPTH is a well-known inhibitor of sclerostin expression in osteocytes. Rodent studies, and recent clinical studies in patients with DM and primary hyperparathyroidism, have reported a negative relationship between serum iPTH and sclerostin [32]. However, in the present study, we did not observe a significant correlation between iPTH and sclerostin in CKD patients prior to dialysis, which is similar to the results reported previously by Pelletier et al.[11] and Morena et al.[24]. In the present study, the suppressive effect may be masked by the low levels of iPTH in the early stages of CKD and in elderly CKD patients. In advanced CKD patients, both sclerostin and iPTH levels are known to increase; this suggests that osteocytes may become resistant to the suppressive effect of iPTH. Furthermore, there are other factors known to directly or indirectly regulate sclerostin, such as phosphorus and fibroblast growth factor 23 (FGF23) in CKD [33, 34]. It is also possible that sclerostin may be upregulated by other unknown regulators under uremic conditions.

This study had several limitations that need to be considered. First, this was a cross-sectional study with a relatively small sample size; we were unable to provide clear evidence of any causality between sclerostin and atherosclerosis. In addition, our study only involved a single center in China; this limits the generalizability of the findings to other ethnicities. Furthermore, our dataset lacked histopathological data from atherosclerotic plaques.

Conclusions

In conclusion, our results indicated that sclerostin increased with the deterioration of renal function in patients with CKD 3–5ND, and that sclerostin plays a crucial role in the development of atherosclerosis. Sclerostin may therefore represent an early warning indicator of atherosclerosis and mortality in patients with CKD.

Abbreviations

ALP, alkaline phosphatase; BMI, body mass index; CKD, Chronic Kidney Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration Equation; CKD-MBD, chronic kidney disease–mineral bone disorder; CKD-ND, non-dialysis patients with chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; FGF23, fibroblast growth factor; HD, hemodialysis; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; IDMS, isotope dilution mass spectrometry; IMT, intima-media thicknesses; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; LRP6, low-density lipoprotein receptor-related proteins 6; OR, odds ratio; SD, standard deviation; VSMCs, vascular smooth muscle cells.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Beijing Hospital (Ethical approval number: 2014BJYYEC-058-01). Written informed consent was obtained from all patients.

Consent for publication

Written informed consent was obtained from all patients.

Availability of data and material

All data generated or analyzed during this study are included in this article. The original dataset is available as Supplementary Material.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BZ designed the experiments, performed the experiments, collected the data, performed the formal analysis and wrote the manuscript. AC designed the experiments, performed the experiments, collected the data, performed the formal analysis. HW, JC, YS and LX performed the experiments and collected the data. YM designed the experiments and reviewed/edited the manuscript.

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Tables

Table 1. Demographic and clinical characteristics of the patients involved in this study along with comparisons between patients in the high and low sclerostin groups.

Variable	All patients n =140	Sclerostin < 46.76 pmol/L n = 70	Sclerostin > 46.76 pmol/L n = 70	P value
Age, years	64 (51, 73)	64 (49, 74)	64 (52, 73)	0.995
Male, n (%)	72, (51.4%)	27, (38.6%)	45, (64.3%)	0.002
Diabetes, n (%)	60, (44.3%)	29, (41.4%)	31, (44.3%)	0.733
Hypertension, n (%)	120, (85.7%)	57, (81.4%)	63, (90.0%)	0.147
Atherosclerotic plaque, n (%)	104, (74.3%)	50, (71.4%)	54, (77.1%)	0.439
Smoker, n (%)	38, (27.1%)	16, (22.9%)	22, (31.4%)	0.254
BMI, (kg/m^2)	24.82 ± 3.91	25.00 ± 3.46	24.65 ± 4.33	0.601
Systolic BP, (mmHg)	130（130, 150）	133（130, 150）	130（130, 150）	0.594
Diastolic BP, (mmHg)	80（70, 86）	80（70, 90）	80（70, 80）	0.266
eGFR, mL/min/1.73 m^2	24.9 (10.0, 40.3)	26.8 (14.3, 44.3)	22.0（8.0, 36.8）	0.020
Hemoglobin, g/L	110 ± 25	115 ± 23	104 ± 26	0.008
Albumin, g/L	40 (37, 43)	41 (38, 43)	40 (36, 42)	0.050
Phosphate, mmol/L	1.37 (1.17, 1.68)	1.32 (1.18, 1.52)	1.45 (1.16, 1.82)	0.042
iPTH, pg/mL	85 (47, 189)	79 (45, 179)	103 (50, 207)	0.161
Alkaline phosphatase, U/L	75 (59, 92)	81 (59, 97)	67 (59, 83)	0.034
Calcium, mmol/L	2.23 (2.10, 2.34)	2.28 (2.16, 2.34)	2.18 (2.00, 2.32)	0.007
Uric acid, umol/L	442 ± 126	424 ± 117	460 ± 133	0.086
Cholesterol, mmol/L	4.31 ± 0.95	4.37 ± 0.98	4.25 ± 0.93	0.429
LDL-C, mmol/L	2.54 ± 0.75	2.56 ± 0.71	2.52 ± 0.78	0.738
HDL-C, mmol/L	1.08 (0.91, 1.28)	1.13 (0.91, 1.35)	1.07 (0.91, 1.25)	0.528
hs-CRP, mg/dl	1.84 (0.85,	1.84 (0.61, 4.13)	1.82 (0.86, 6.94)	0.250

	4.67)

Normally distributed variables are shown as mean ± standard deviation; non-normally distributed variables are shown as medians (with 25 and 75% interquartile ranges in parentheses). *BMI,* body mass index; *eGFR,* estimated glomerular filtration rate; *iPTH,* intact parathyroid hormone; *LDL-C,* low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *hs-CRP,* high-sensitivity C-reactive protein.

Table 2. Comparisons between patients with and without atherosclerotic plaques.

Variable	Patients with plaques n = 104	Patients without plaques n = 36	P value
Age, years	67.0 (61.0, 74.0)	44.5 (35.3, 55.3)	< 0.001
Male, n (%)	58, (55.8%)	14, (38.9%)	0.081
Diabetes, n (%)	54, (51.9%)	6, (16.7%)	< 0.001
Hypertension, n (%)	94, (90.4%)	26, (72.2%)	0.007
Smoker, n (%)	32, (30.8%)	6, (16.7%)	0.101
BMI, (kg/m^2)	25.35 ± 3.72	23.31 ± 4.11	0.007
Systolic BP, (mmHg)	130□130, 150□	137□130, 150□	0.896
eGFR, mL/min/1.73 m^2	11.8 (27.0, 40.7)	5.6□18.3, 38.0□	0.069
Hemoglobin, g/L	113 ± 23	101 ± 27	0.013
Albumin, g/L	41 (38, 43)	40 (37, 43)	0.517
Phosphate, mmol/L	1.37 (1.11, 1.60)	1.39 (1.19, 1.92)	0.107
iPTH, pg/mL	77.9 (46.0, 172.3)	114.5 (58.0, 243.8)	0.037
Alkaline phosphatase, U/L	75 (59, 93)	74 (57, 91)	0.543
Calcium, mmol/L	2.26 (2.13, 2.34)	2.17 (1.97, 2.33)	0.144
Uric acid, umol/L	418.8 ± 107.3	509.7 ± 150.8	0.002
Cholesterol, mmol/L	4.26 ± 0.94	4.46 ± 0.99	0.265
LDL-C, mmol/L	2.51 ± 0.75	2.64 ± 0.75	0.379
HDL-C, mmol/L	1.07 (0.92, 1.28)	1.13 (0.89, 1.35)	0.894
hs-CRP, mg/dl	1.80 (0.83, 5.07)	2.02 (1.20, 3.73)	0.635
Sclerostin, (pmol/L)	47.66 (32.60, 72.91)	42.62 (26.20- 55.50)	0.010

Normally distributed variables are shown as mean ± standard deviation; non-normally distributed variables are shown as medians (with 25 and 75% interquartile ranges in parentheses). *BMI,* body mass index; *eGFR,* estimated glomerular filtration rate; *iPTH,* intact parathyroid hormone; *LDL-C,* low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *hs-CRP,* high-sensitivity C-reactive protein.

Table 3. Factors related to carotid atherosclerotic plaques.

Variable	Coefficient(r) or β	P	OR (OR 95% CI)
Age (per year)	0.127	< 0.001	1.136 (1.082, 1.192)
BMI, (kg/m^2)	0.157	0.049	1.170 (1.000, 1.369)
Diabetes (Y versus N)	1.125	0.046	3.372 (1.020, 11.142)
Sclerostin (1 pmol/L)	0.026	0.029	1.026 (1.003, 1.051)

BMI, body mass index; *OR*, Odds ratios; *CI*, confidence interval.

Figures

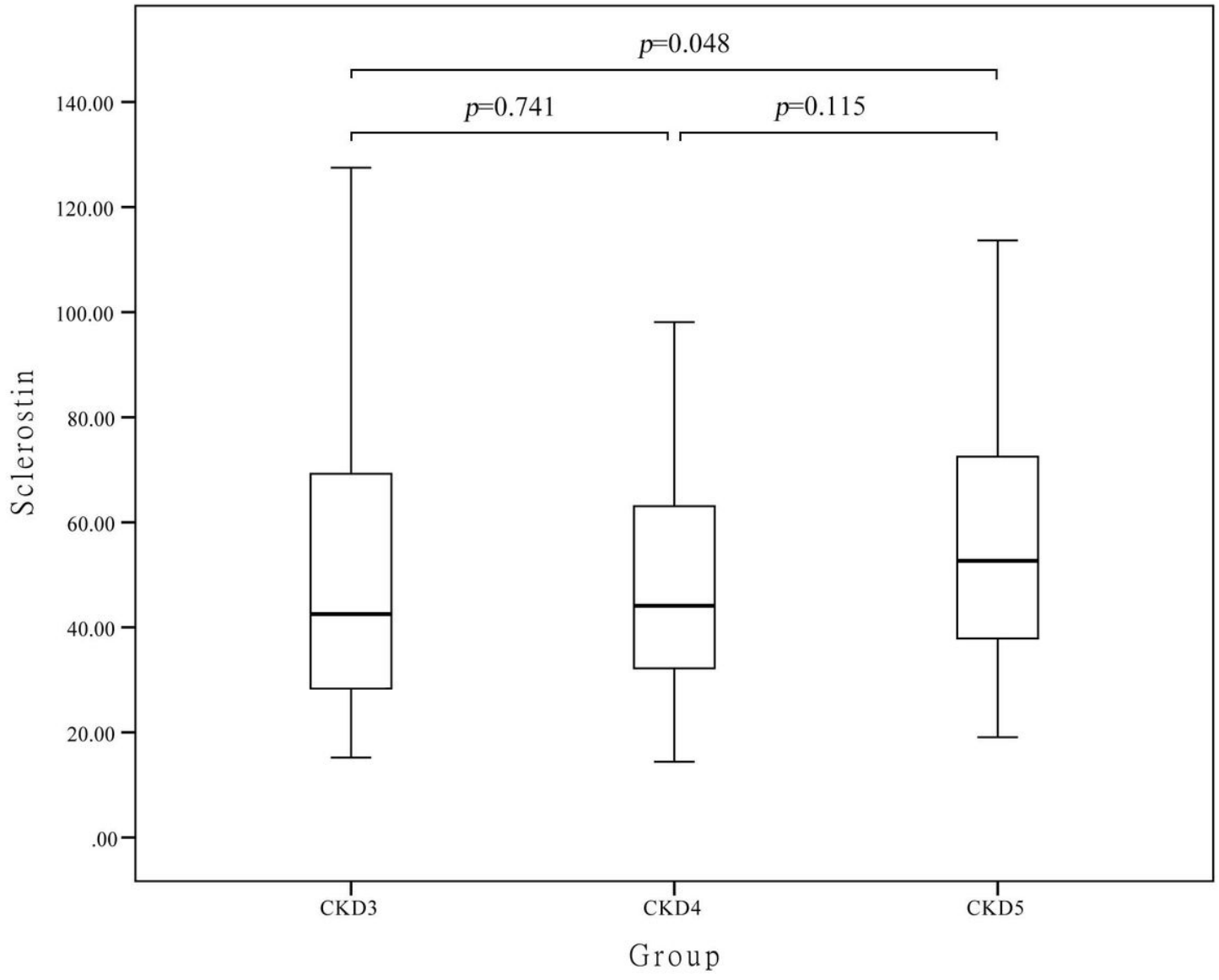

Figure 1

Comparison of serum sclerostin between patients in CKD 3, 4 and 5 stages.

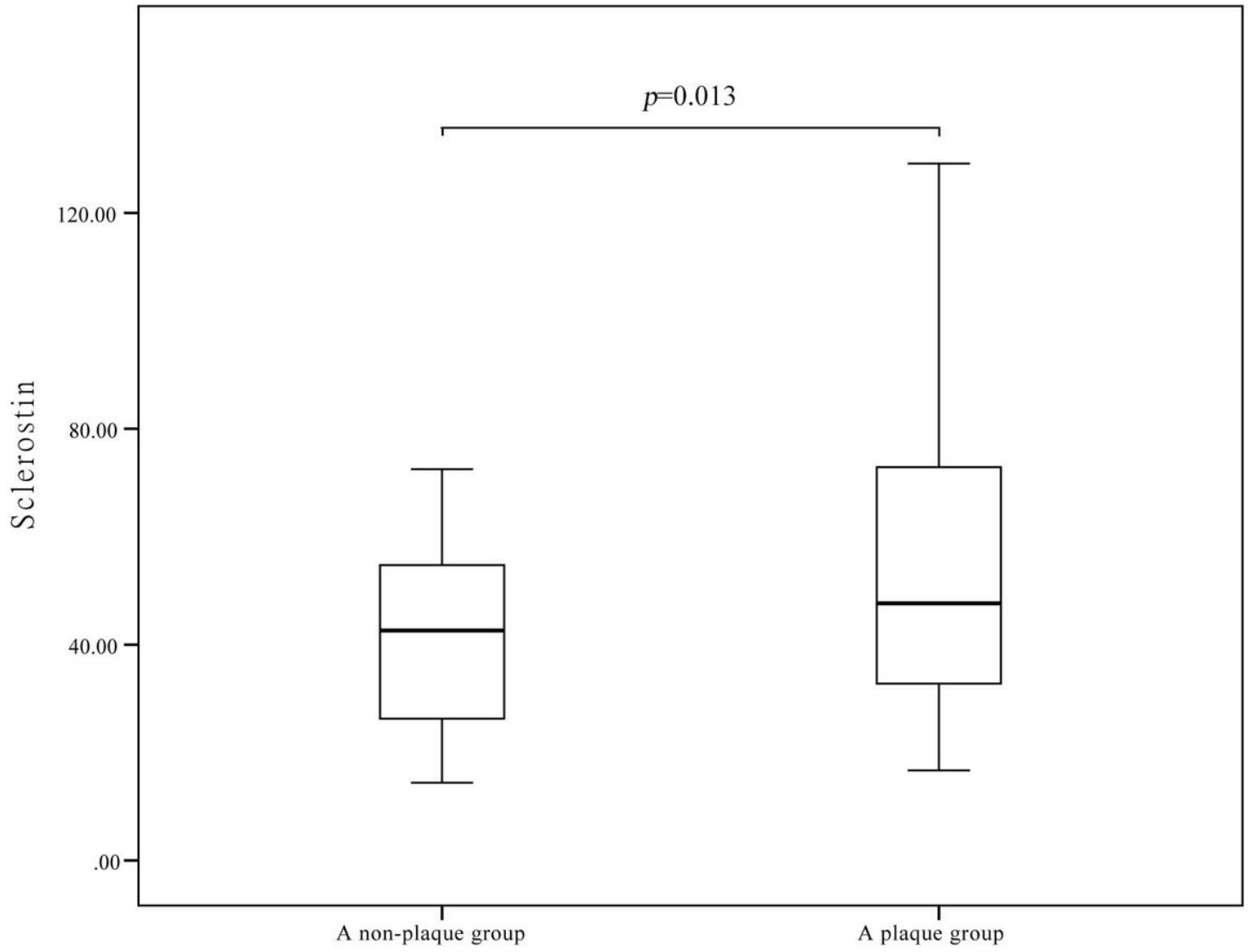

Figure 2

Comparison of serum sclerostin between patients in the plaque group and the non-plaque group.

Supplementary Files

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- Additionalfile1.xlsx