# Decreased circulating sclerostin levels in renal transplant recipients with persistent hyperparathyroidism[1]

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**Abbrevations**:

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HPT: hyperparathyroidism, PTH: parathyroid hormone

## ABSTRACT

**BACKGROUND**: Sclerostin is an osteocyte-secreted soluble antagonist of the Wnt/β-catenin signaling pathway requisite for osteoblast development and activity. The regulation of sclerostin expression in bone is complex. Parathyroid hormone (PTH) is recognized to be an important suppressor. Circulating sclerostin levels are 2 to 4-fold higher in patients with end stage renal disease as compared to individuals with normal renal function. **METHODS**: We performed a longitudinal observational cohort study and case-control study in 50 *de novo* renal transplant recipients, 50 CKD patients (n=50) matched for age, gender and eGFR, and 23 renal transplant recipients referred for parathyroidectomy to define the impact of renal transplantation on circulating sclerostin levels and to clarify the role of persistent (tertiary) hyperparathyroidism. **RESULTS**: Sclerostin serum levels decreased by 61.2 % (median) during the first 3 month after transplantation (1.24 vs 0.44 ng/ml, $p<0.0001$) to increase thereafter towards levels observed in CKD counterparts (0.63 ng/ml). High PTH levels independently associated with low sclerostin levels, both at time of transplantation and at 1 year. Sclerostin levels significantly increased following parathyroidectomy (0.49 vs. 0.32 ng/ml, $p<0.0001$). The time course of bone biomarkers after parathyroidectomy suggests that bone resorption normalizes earlier than bone formation. **CONCLUSIONS**: Circulating sclerostin levels appear to show a biphasic pattern after renal transplantation with a rapid and profound decrease, followed by gradual increase towards levels observed in CKD counterparts. Our data support the notion that PTH is an important regulator of circulating sclerostin levels.

**INTRODUCTION**

Sclerostin is a glycoprotein, coded for by the *SOST* gene [MIM 269500], produced almost exclusively by osteocytes. Secreted sclerostin inhibits Wnt/β-catenin signaling, a pathway with major importance in bone biology. Humans with inactivating sclerostin mutations have significantly increased bone formation rates[1]. Present understanding of the regulation of SOST expression by osteocytes is expanding but is as yet incomplete[2]. Calcitonin[3], TNF-α[4], and probably also BMP2, 4, and 6 are able to stimulate SOST expression, while mechanical loading[5], and parathyroid hormone (PTH)[6] have been shown to decrease SOST mRNA.

Serum sclerostin levels increase along the progression of renal failure to reach levels that are 3 to 4-fold higher in patients with end stage renal disease as compared to non-renal controls[7-9]. Increased production, rather than to decreased renal elimination seems to account for the increased sclerostin levels in chronic kidney disease (CKD) [10;11].

Only few studies so far studied the impact of renal transplantation on circulating sclerostin levels. In a small cross-sectional study, circulating sclerostin levels in 19 renal transplant recipients were found to be similar to levels observed in CKD patients matched for age and renal function[12]. Bonani *et al.* prospectively monitored circulating sclerostin levels in 42 de novo renal transplant recipients and observed a rapid decline paralleling the recovery of renal function[13]. None of these studies however focused on the interaction between PTH and sclerostin levels in the posttransplant setting. While PTH resistance may be hypothezised to rapidly wane after renal transplantation parallel to the recovery of renal function, the involution of hyperplastic parathyroid glands is slow. PTH levels thus may become

inappropriately high in a substantial proportion of de novo renal transplant recipients, a condition commonly referred to as persistent or tertiary hyperparathyroidism (HPT)[14].

The present study aimed (a) to elucidate the natural history of circulating sclerostin levels after renal transplantation and (b) to clarify the association between circulating levels of sclerostin and PTH in the setting of renal transplantation.

## MATERIAL AND METHODS

### *Study design and population*

This is a post-hoc analysis on data and serum samples collected in the frame of ongoing prospective observational cohort studies addressing various aspects of CKD-MBD across all stages of disease.

The natural posttransplant history of circulating sclerostin levels was studied in 50 *de novo* renal transplant recipients (RTRs) (NCT00547040). Baseline demographics and relevant biochemistry of RTRs enrolled in the present study did not differ from unselected renal transplant recipients (n=107) transplanted in the same period (April 2007 until July 2008) (data not shown).

To determine how circulating sclerostin levels in *de novo* renal transplant recipients compare to levels observed in non-transplanted CKD patients, we also included a control group of CKD patients (n=50), matched (1:1) for age, gender and estimated glomerular filtration rate (eGFR) at month 12. These controls were selected manually from the Leuven mild-to-moderate CKD cohort (NCT00441623) by one investigator (PE) masked for other clinical and biochemical parameters. Each control was used only once.

To further elucidate the impact of persistent hyperparathyroidism on circulating sclerostin levels, 23 RTRs with severe persistent hyperparathyroidism were investigated before and after the parathyroidectomy (PTX) (NCT00452049).

All studies adhere to the principles of the Declaration of Helsinki and were approved by the ethical committee of the University Hospitals Leuven. All patients provided informed consent.

***Data collection***

In *de novo* RTRs, serum samples were collected immediately before transplantation [baseline] (random, nonfasting) and at day 7, month 3 (M3) and 12 (M12) post-transplantation (fasting). In CKD patients, serum samples were collected during a routine follow-up outpatient visit (random, nonfasting). In RTRs with severe persistent HPT referred for PTX, serum samples (fasting) were obtained before the procedure and at the time of discharge at day 11.7 [4.0-18.6]. In half of these patients, serum samples could also be obtained 7.4 [6.0-9.6] months after the procedure. All samples were stored for <2 h at 5°C until centrifugation. Upon arrival at the laboratory, the blood samples were centrifuged at 3000 rpm for 10 min, distributed in aliquots, and stored at –80°C until analysis.

Relevant demographics and clinical data, as well as therapy details were extracted from the prospectively collected electronic medical data files.

Serum creatinine, (ionized) calcium, phosphorus, and immunosuppressive drug trough levels were measured using standard assays. Serum 1,25-dihydroxyvitamin D (calcitriol) and 25-hydroxyvitamin D (calcidiol) levels were measured using a RIA[15;16]. Serum full-length *(bio-intact)* PTH levels were determined by an immunoradiometric assay, as described elsewhere[17]. Serum sclerostin (TECOmedica; Demeditec Diagnostics GmbH, Kiel-Wellsee,

Germany) and full-length Fibroblast Growth Factor 23 (FGF23, Kainos Lab, Japan) were measured by ELISA, according to the manufacturer's instructions. The limit of detection of the sclerostin assay is 0.015 ng/mL (multiply by 0.044 to convert to pmol/L); the lower and upper limit of quantification are, respectively 0.17 and 4.88 ng/mL. Bone-specific alkaline phosphatase (bsAP), as a measure of bone formation, was determined using an electrophoretic method (ISOPAL; Analis, Sint-Denijs-Westrem, Belgium). To assess bone resorption, serum C-terminal cross-linked telopeptide was measured using an electrochemiluminescence immunoassay (b-CrossLaps/serum; Roche Diagnostics, Basel, Switzerland). The eGFR was calculated using the short Modification of Diet in Renal Disease formula.

### *Statistics*

Continuous variables are expressed as means (SD) for normally distributed variables or median (minimum–maximum) otherwise. Differences between periods were analysed using paired t-test or signed rank test, as appropriate. Differences between groups were analyzed using a nonparametric 1-way ANOVA (Wilcoxon) or $Chi^2$, as appropriate. Associations between serum sclerostin and clinical and biochemical parameters were studied with Spearman rank correlation and univariate and multivariate linear regression. Parameters that were not normally distributed, including sclerostin, were log-transformed. The SAS version 9.2 (SAS Institute, Cary, North Carolina) software program was used for the statistical analysis. Two-sided P values <.05 were considered statistically significant.

## RESULTS

### *Patient characteristics*

Relevant demographics and primary renal disease of patients enrolled in the present study are summarized in ***table 1.*** Maintenance immunosuppression at M3 consisted of corticosteroids, a calcineurin inhibitor (tacrolimus, 76% or cyclosporine, 24 %) and an antimetabolite (mycophenolate mofetil). Cumulative methylprednisolone exposure amounted to 0.65±0.21, 1.51±0.46, and 2.49±0.79 g at day 7, M3 and M12, respectively. In 13 patients, therapy with steroids was halted between M3 and M12. Cyclosporine and tacrolimus dosing was concentration controlled according to standard protocols. A substantial number of patients were treated with nutritional and/or active vitamin D. Calcimimetics were interrupted in all patients at the time of transplantation (n=11). In one patient, calcimimetic treatment was initiated between M3 and M12. Finally, 12% of patients were treated with bisphosphonates at M3 and M12.

***Time course of circulating sclerostin levels after renal transplantation***

***Table 2*** shows the time course of laboratory parameters of mineral metabolism and circulating sclerostin levels after renal transplantation. In agreement with literature data, PTH levels sharply decreased, while calcitriol levels markedly increased during the first 3 months following transplantation. These changes were accompanied by a significant increase of serum calcium levels and a drop of serum phosphorus levels. Between M3 and M12, PTH and calcitriol levels showed changes in the same direction, but at a much slower pace. Hyperparathyroidism at M12, defined by a PTH levels above upper normal limit, with and without hypercalcemia was observed in 20.3 and 28.1%, respectively. Serum sclerostin decreased by on average 61.2% [54.6-68.5%] between baseline and M3. Remarkably, serum sclerostin level increased again between M3 and M12, on average by 24.4% [2.0-40.8%]. Of note, the increase of sclerostin between M3 and M12 significantly correlated with the decrease of PTH in the same period (p=0.007). Results were similar in patients free of either

bisphosphonates or glucocorticoids at M12 (data not shown). RTRs had significantly higher serum levels of calcium and PTH at M12, as compared to CKD counterparts, while sclerostin levels tended to be lower (p=0.08). Calcitriol levels did not differ between the two groups. Calcidiol levels tended to be higher in RTRs (p=0.05).

***Factors associated with circulating sclerostin levels in de novo renal transplant recipients***

***Table 3*** summarizes the results of the regression analysis in RTRs at M12. In univariate regression analysis, higher age and calcidiol, lower calcitriol, PTH, and eGFR and male gender were all significantly associated with higher sclerostin. In multivariate analysis, only male gender, lower eGFR and lower PTH were significantly associated with higher sclerostin. These variables explain 38% of the variation of circulating sclerostin ($R^2$=0.38, p<0.0001)..

***Sclerostin levels in renal transplant recipients before and after parathyroidectomy***

To further clarify the impact of PTH on circulating sclerostin levels, we monitored laboratory parameters of CKD-MBD and circulating sclerostin levels in 23 RTRs with severe persistent/tertiary HPT before and after PTX ***(table 4)***. Demographics and primary renal disease of patients enrolled in this substudy are summarized in ***table 1.*** PTX was timed on average 11.7 [3.9-18.6] months after renal transplantation. As expected, serum levels of PTH and calcium decreased, while serum phosphorus levels significantly increased following PTX. Importantly, sclerostin levels significantly increased early after the PTX (by 0.15 [0.06-0.22]ng/ml, p<0.0001). Not unexpectedly, patients with severe persistent HPT showed increased bone specific alkaline phosphatase (bsAP, bone formation marker) and β-CTX levels (marker of bone resorption), similar to what has been observed in primary hyperparathyroidism[18]. Bone turnover markers decreased following PTX, with the decrease of β-CTX preceding the decrease of bsAP. Results were similar in a subgroup of patients in

whom kidney function did not deteriorate following PTX, defined by eGFR decline <5 ml/min 1.73m² (results not shown).

## DISCUSSION

Our data demonstrate that circulating sclerostin levels (a) rapidly decline following renal transplantation and (b) are suppressed in renal transplant recipients with persistent/tertiary hyperparathyroidism.

Circulating sclerostin levels rapidly decline following renal transplantation, parallel to the recovery of renal function. After this initial profound drop (by >60%), sclerostin levels showed a slight rebound towards levels observed in CKD patients, matched for gender, age and eGFR. As such, our data confirm and extend previous findings in smaller cohorts[12;13]. Increased renal elimination most probably accounts to a large extent for the rapid decline of circulating sclerostin levels following transplantation observed in the present and previous studies[13]. Due to its relatively low molecular mass (~28 kDa for the glycosylated protein), positive charge and rod-like structure, sclerostin is likely to be filtered across the glomerular membrane[10]. In physiological conditions, most of this filtered sclerostin, is reabsorbed in the proximal tubule[10]. In the early posttransplant period, a high filtered load and/or tubular dysfunction (related to ischemia-reperfusion injury) may induce so-called overload proteinuria resulting in the losses of substantial amounts of sclerostin in the urine. Interestingly, the fractional excretion of sclerostin has previously been shown to strongly correlate with the fractional excretion of α1-microglobulin, a marker of tubular injury[10].

Suppressed sclerostin production, mediated by inappropriately high PTH levels, most probably also contributes to the low circulating sclerostin levels the early posttransplant period. Sclerostin levels tended to be lower, while PTH levels were higher in *de novo* renal transplant recipients as compared to CKD counterparts. PTH was the only laboratory

parameter of mineral metabolism that showed a significant and independent association with circulating sclerostin levels. Moreover, in *de novo* RTRs with severe persistent (tertiary) HPT circulating sclerostin levels significantly increased following parathyroidectomy. Our data corroborate data from observational studies in patients with primary HPT[18-20] and intervention studies in non-renal subjects[21;22]. In the latter studies, decreased serum sclerostin levels were demonstrated in individuals administered intermittent[21] or continuous[22] recombinant PTH. Altogether, these data support the hypothesis that PTH is an important regulator of circulating sclerostin levels. Whether PTH directly affects sclerostin expression and secretion or indirectly mediates changes by altering bone turnover remains to be investigated. Our data indicate that suppressed sclerostin levels may represent another manifestation of persistent (tertiary) HPT, next to hypophosphatemia and hypercalcemia[14]. Low sclerostin levels in patients with HPT may be hypothezised to represent a compensatory feedback mechanism aimed at limiting bone loss by stimulating bone formation in the face of relentless bone resorption.

Glucocorticoids have been shown to increase the expression of sclerostin in experimental studies[23]. In a recent clinical study, however, the impact of glucocorticoids on circulating sclerostin levels proved to be modest at best and to depend on both the doses and duration of the therapy[24]. In the present study, no association was found between cumulative glucocorticoids dose and sclerostin levels. Moreover, since sclerostin levels in *de novo* renal transplant recipients were lower than in steroid naïve CKD counterparts, it may be concluded that at least in the setting of impaired renal function the impact of glucocorticoids is marginal.

The slight rebound of circulating sclerostin levels between month 3 and 12 may be explained either by restoration of renal tubular function or recovery of persistent hyperparathyroidism.

The latter is supported by the significant correlation between delta sclerostin and delta PTH observed within this time frame. In agreement with published data in CKD patients [7;8;10;25], serum sclerostin levels inversely associated with renal function in RTRs.

It is well established that in hyperparathyroid states (chronic excess of PTH), the bone anabolic actions of PTH are overridden by its RANKL-mediated catabolic actions. In line with this, especially bone resorption markers were increased in patients with severe persistent/tertiary HPT. Following parathyroidectomy, sclerostin levels returned towards normal and bone resorption markers rapidly decreased. The decrease of bone resorption markers preceded the decrease of bone formation markers. These observations confirm and extend findings in parathyroidectomized patients with primary HPT [18].

Mounting evidence indicates that sclerostin may quality as a novel biomarker of CKD-Mineral and Bone Disorder (CKD-MBD)[26]. Circulating sclerostin levels associate with indices of bone and vascular health and with mortality in CKD patients [7;8;25;27-31]. Also in the setting of renal transplantation, the assessment of the circulating sclerostin level may prove useful. One of the characteristics of an ideal biomarker is that information gleaned by measurement should add to, or improve upon existing tests, aid risk assessment or enhance patient management. Measuring of sclerostin levels in renal transplant recipients presenting with high PTH level may help differentiating between secondary HPT and persistent (tertiary) HPT. A low sclerostin level may point to persistent HPT as the most probable diagnosis and as such identify patients that may benefit most from either parathyroidectomy or calcimimetic therapy. Self-evidently, additional studies, including bone biopsies are required for confirmation and to establish diagnostic cut-off values.

The present study has several strengths, including the availability of broad panel of laboratory parameters of bone and mineral metabolism, prospectively collected, before and after renal transplantation and before and after parathyroidectomy. The study should however also be interpreted within its limitations. These include rather small sample size, limited number of sampling time points after transplantation and missing bone phenotype data (dual-energy X-ray absorptiometry, bone histomorphometry).

In conclusion, circulating sclerostin levels appears to show a biphasic pattern after renal transplantation with a rapid decrease, followed by gradual increase towards levels observed in CKD counterparts. Persistent hyperparathyroidism associates with low sclerostin levels. Additional studies are required to validate sclerostin as a clinically useful biomarker of CKD-MBD.

**FIGURE LEGENDS :**

**Figure 1** : Circulating sclerotin levels in *de novo* renal transplant recipients (n=50) and CKD patients, matched for gender, age and eGFR (n=50)

**Figure 2** : Levels of PTH (A), sclerostin (B), β-CTX (C) en bsAP (D) in 23 renal transplant recipients immediately before parathyroidectomy (pre), and 11.7 [4.0-18.6] days (post, early) and 7.4 [6.0-9.6] months (post, late) after the procedure. NS, not significant

**Table 1**: Demographics

| | RTR, *de novo* (n=50) | RTR, pHPT (n=23) | CKD (n=50) |
|---|---|---|---|
| Time on dialysis (m) | 40.7 [24.3-55.7] | 53.4 [30.5-64.8] | - |
| Age | 52.9 ± 10.3 | 52.9 ± 10.8 | 53.6 ± 9.2[NS] |
| Sex, male (%) | 70 | 44 | 72 [NS] |
| Weight (kg) | 72.1 ± 13.7 | 78.7 ±21.3 | 81.8 ± 19.1[a] |
| Length (m) | 1.71 ± 0.09 | 1.71 ± 0.18 | 1.73 ± 0.10 [NS] |
| Body Mass Index (kg/l$^2$) | 24.7 ± 4.0 | 24.9 ± 4.4 | 26.7 ± 4.8[a] |
| Diabetes (%) | 16 | 39 | 14 [NS] |
| Renal diagnosis (%) | | | [NS] |
| Diabetic nephropathy | 10 | 4 | 0 |
| Glomerulonephritis /vasculitis | 34 | 30 | 44 |
| Interstitial nephritis | 4 | 0 | 4 |
| Hypertensive/large vessel disease | 2 | 4 | 0 |
| Cystic/hereditary/congenital diseases | 30 | 39 | 22 |
| Miscellaneous, unknown or missing | 20 | 22 | 30 |

NS: not significant; [a]. p<0.05 CKD vs. RTR, de novo

**Table 2**: Laboratory parameters of mineral metabolism, serum sclerostin levels, and therapy in *de novo* RTRs and CKD counterparts (n=50)

| | **TX** | **D7** | **M3** | **M12** | **CKD** | **P CKD vs M12** |
|---|---|---|---|---|---|---|
| eGFR (ml/min/1.73m²) | - | 37.1 ± 20,9 | 48.0 ± 17.3[-] | 52.4 ± 14.7[x] | 48.9 ± 18.7 | NS |
| Creatinine (mg/dL) | 8.3 ± 2.6 | 2.90 ± 2.42 | 1.57 ± 0.50[c] | 1.42 ± 0.40[z] | 1.58±0.56 | NS |
| Calcium total (mg/dL) | 9.01 ± 0.86 | 8.8 ± 0.9 | 9.6 ± 0.7[c] | 9.6 ± 0.7[NS] | 9.2 ± 0.4 | 0.002 |
| Calcium ionized (mmol/L) | NA | NA | 1.33 ± 0.11[-] | 1.30 ± 0.08[NS] | NA | - |
| Phosphorus (mg/dL) | 4.7 ± 1.5 | 3.1 ± 1.8 | 2.6 ± 0.6[c] | 2.9 ± 0.5[y] | 3.1 ± 0.6 | NS |
| Bicarbonate (mmol/L) | 23.9 ± 3.5 | NA | 23.0 ± 2.7[NS] | 23.6 ± 2.9[NS] | 24.8 ± 4.4 | NS |
| Biointact PTH (ng/L) | 116.2 [74.8 - 236.1] | NA | 52.5 [33.5 - 80.0][c] | 38.7 [24.6 - 55.0][x] | 22.7 [14.5-36.9] | 0.004 |
| Calcidiol (µg/L) | 34.7 ± 17.2 | NA | 24.5 ± 10.1[c] | 30.1 ± 13.9[y] | 24.8 ± 12.6 | NS (0.05) |
| Calcitriol (ng/L) | 24.45 [17.8 - 31.6] | NA | 41.1 [34.9 - 45.8][c] | 42.3 [34.5 - 53.5][x] | 50.2 [35.3-59.2] | NS |
| Sclerostin (ng/mL) | 1.24 [0.81 - 1.47] | 0.49 [0.37 - 0.66] | 0.44 [0.35 - 0.59][c] | 0.53 [0.41-0.75][z] | 0.63 [0.48-0.86] | NS (0.08) |
| Biointact FGF23 (ng/mL) | 2849 [758-5417] | NA | NA | 85 [55-114] | 64 [50-91] | NS |
| Alkaline phosphatase (U/L) | 223.3 ± 99.6 | 187.7 ± 77.0 | 189.0 ± 100.7[b] | 195.8 ± 85.5[NS] | 190.0 ± 140.0 | NS |
| C-reactive protein (mg/L) | 3.4 [6.9-25.5] | NA | 1.0 [1.0-2.2][c] | 1.7 [1.0-6.1][NS] | 1.4 [0.6-4.3] | NS |
| Glucocorticoids (%) | 0 | 100 | 100 | 81 | *14* | <0.05 |
| Cum GC exposure (g) | 0 | 0.7 ± 0.2 | 1.5 ± 0.5 | 2.5 ±0.8 | - | - |
| Native VitD (%) | 48 | 0 | 20 | 38 | 26 | NS |
| Active VitD (%) | 54 | 0 | 25 | 26 | 8 | <0.001 |
| Calcimimetics (%) | 16 | 0 | 0 | 2 | 0 | NS |
| CCPB-Ca supplement(%) | 88 | 0 | 38 | 38 | 16 | 0.02 |
| non-CCPB (%) | 48 | 0 | 0 | 0 | 0 | NS |
| Bisphosphonates (%) | 0 | 0 | 12 | 12 | 0 | 0.01 |

NS: non-significant; CCPB: calcium-containing phosphate binder; GC: glucocorticoids

[a.] <0.05; [b]. <0.01; [c.] <0.001 TX vs M3

[x]. <0.05; [y.] <0.01; [z.] <0.001 M3 vs M12

Conversion factors for units: serum creatinine in mg/dL to mol/L, ×88.4; phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495; 25(OH)D in μg/L to nmol/L, ×2.496; 1,25(OH)2D in ng/L to pmol/L, ×2.6

**Table 3**: Clinical and biochemical parameters at M12 associated with circulating sclerostin level.

| | B | p | $R^2$ |
|---|---|---|---|
| Independent variables (unit) | | | |
| **Univariate analysis** | | | |
| Age | 0.006 | 0.02 | 0.11 |
| Gender (male 1; female 0) | 0.16 | 0.003 | 0.17 |
| logFGF23 | 0.16 | 0.10 | 0.05 |
| eGFR | -0.004 | 0.04 | 0.09 |
| Calcidiol | 0.005 | 0.02 | 0.12 |
| LogCalcitriol | -0.51 | 0.009 | 0.14 |
| LogPTH | -0.15 | 0.005 | 0.16 |
| Glucorticoids (on 1; off 0) | -0.13 | 0.06 | 0.08 |
| **Multivariate analysis** | | <0.0001 | 0.38* |
| Age | - | - | |
| Gender (male 1; female 0) | 0.16 | 0.002 | |
| eGFR | -0.004 | 0.009 | |
| LogPTH | -0.12 | 0.01 | |

Parameters evaluated in regression analysis: age, gender, calcium, phosphorus, eGFR, logPTH, logCalcitriol, calcidiol, CRP, BMI, glucocorticoid usage. Only parameters univariately associated at $p \leq 0.2$ are mentioned in the table.
*p-value and $R^2$ for overall model

**Table 4**: Laboratory parameters of mineral metabolism and sclerostin levels in RTRs with severe persistent HPT referred for parathyroidectomy

| | Pre (23) | Post, early (23) | Post, late (12) | P pre vs post, early | P post, early vs post, late |
|---|---|---|---|---|---|
| eGFR (ml/min/1.73m²) | 44.8 ± 12.3 | 39.1 ± 13.2 | 53.3 ± 15.7 | 0.0004 | 0.02 |
| Creatinine (mg/dL) | 1.42±0.39 | 1.65±0.63 | 1.35 ± 0.32 | 0.002 | 0.1 |
| Calcium total (mg/dL) | 10.9±0.7 | 8.7±1.1 | 9.2 ± 1.1 | <0.0001 | 0.07 |
| Calcium ionized (mmol/L) | 1.49 ± 0.12 | 1.15 ± 0.13 | NA | <0.0001 | NA |
| Phosphorus (mg/dL) | 2.1 ± 0.4 | 3.3±0.9 | 2.9 ± 0.8 | <0.0001 | 0.3 |
| Bicarbonate (mmol/L) | 23.3 ± 2.5 | 24.1±2.4 | 25.4 ± 3.2 | 0.1 | 0.2 |
| Biointact PTH (ng/L) | 97.4 [71.1-147.1] | 9.4 [0.1-28.4] | 10.1 [2.2-57.3] | <0.0001 | 0.6 |
| Calcidiol (µg/L) | 26.1±14.3 | 24.5 ± 13.9 | 29.2 ± 16.0 | 0.4 | 0.5 |
| Calcitriol (ng/L) | 57.0 [44.5-67.3] | 49.9 [43.4-60.4] | 54.9 [52.0-59.8] | 1 | 0.3 |
| AP ( U/L) | 228±80 | 230±79 | 159 ± 45 | 0.8 | 0.02 |
| bsAP (U/L) | 75.4±51.0 | 80.7 ± 52.0 | 37.8 ± 17.6 | 0.4 | 0.002 |
| β–CTX (pg/ml) | 789 [573-1269] | 350 [236-685] | 231 [115-407] | <0.0001 | 0.03 |
| Sclerostin (ng/mL) | 0.32 [0.26-0.42] | 0.49 [0.32-0.57] | 0.44 [0.32-0.61] | <0.0001 | 0.5 |

Blood samples were collected immediately before the parathyroidectomy (pre), and 11.7 [4.0-18.6] days (post, early) and 7.4 [6.0-9.6] months (post, late) after the procedure.

Conversion factors for units: serum creatinine in mg/dL to mol/L, ×88.4; phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495;

Figure 1

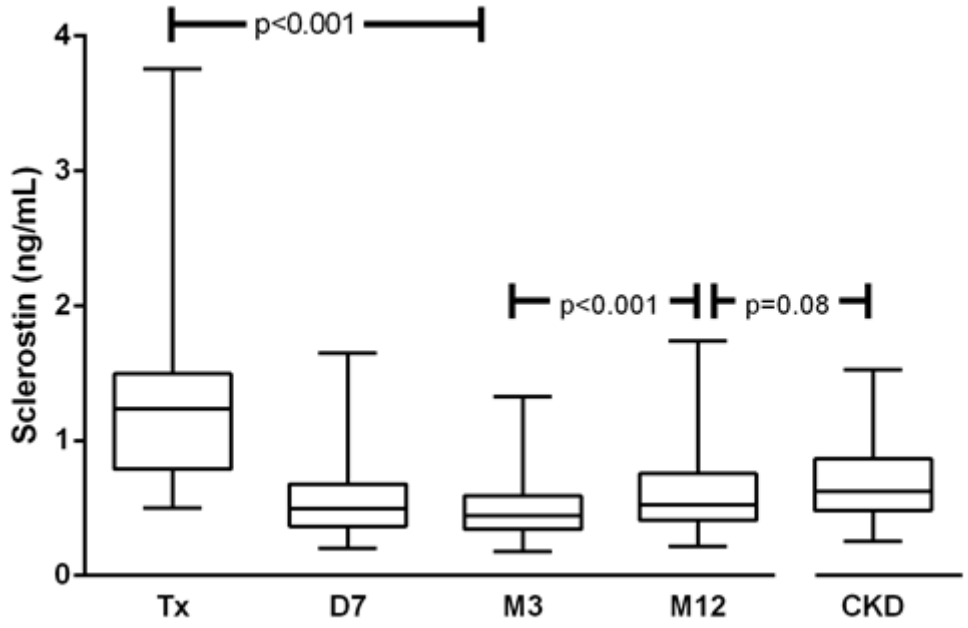
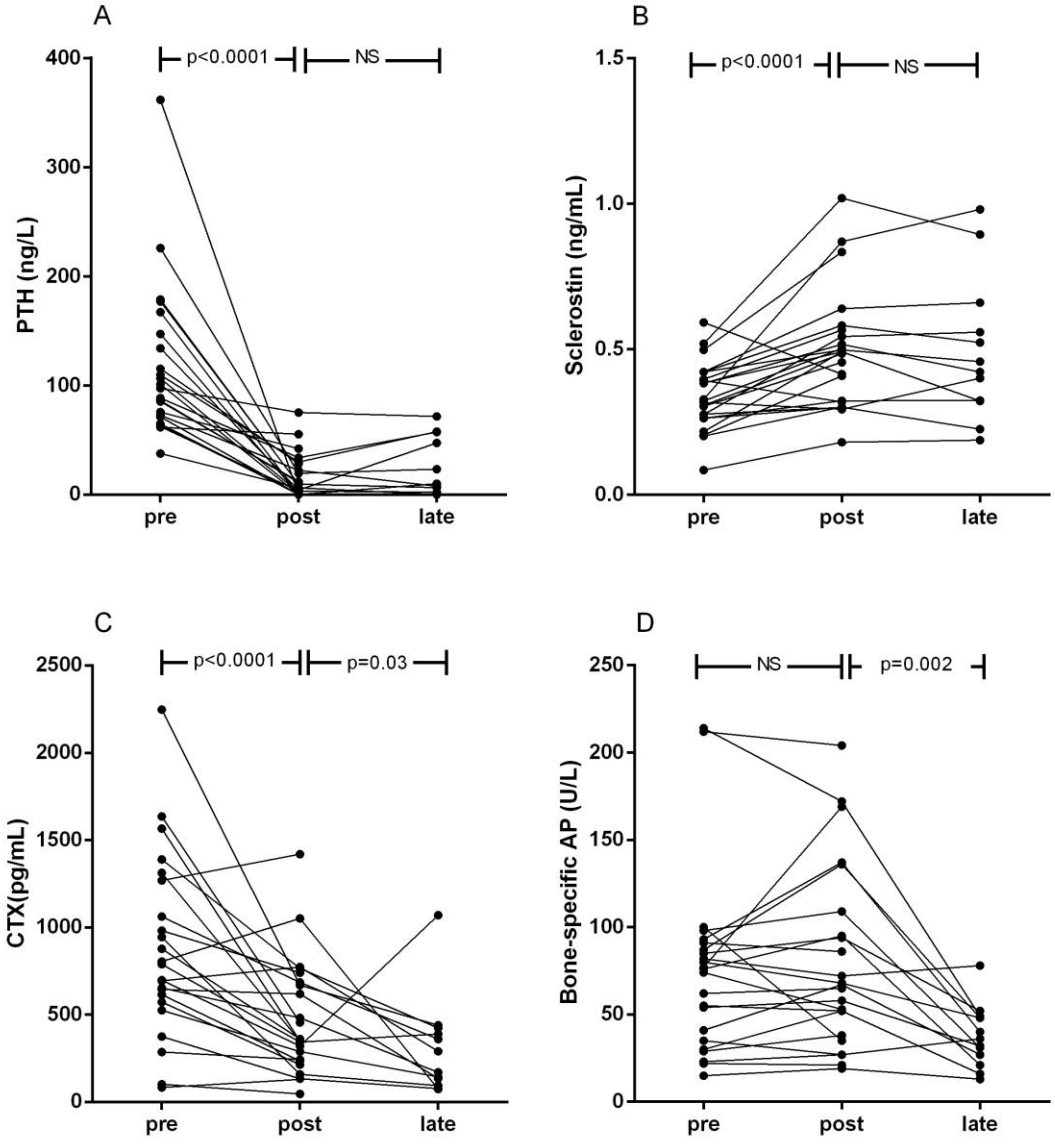


Figure 2


A
p<0.0001
NS
PTH (ng/L)
400
300
200
100
0
pre
post
late
B
p<0.0001
NS
Sclerostin (ng/mL)
1.5
1.0
0.5
0.0
pre
post
late
C
p<0.0001
p=0.03
CTX(pg/mL)
2500
2000
1500
1000
500
0
pre
post
late
D
NS
p=0.002
Bone-specific AP (U/L)
250
200
150
100
50
0
pre
post
late

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