Original Article

EFFECT OF URINARY CALCIUM EXCRETION ON BONE MARKERS IN OSTEOPOROTIC PATIENTS

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Abstract

Background: Urine calcium excretion (UCaE) could reflect calcium balance and bone activities. High UCaE is prevalent among patients with osteoporosis. However, the relationship between UCaE and bone turnover markers is not well-studied.

Methods: Cross-sectional study of post-menopausal women with refractory osteoporosis. Total and ionized calcium, UCaE, estimated GFR, PTH including cyclase activating PTH (CAP); and cyclase inhibitory PTH (CIP), markers of bone formation, osteocalcin and bone-specific alkaline phosphatase (BSAP), and bone resorption, serum N-telopeptide Collagen (NTX) were recorded.

Results: Study included 205 post-menopausal women with mean age of 64±10 years. HTN was found in 36%, while DM in 6%, and 13% of patients had CKD. Kidney stones were recorded in 7%, while 77% of patients had previous fractures. Only 4% of patients had vitamin D deficiency. Serum calcium and phosphorus correlated positively with osteocalcin, while ionized calcium correlated also with NTX. Alkaline phosphatase showed a positive correlation with bone formation markers. Estimated GFR correlated negatively with age, phosphorus, PTH CIP, and NTX, while it correlated positively with UCaE. Urinary calcium did not correlate with bone formation or resorption markers, but it correlated negatively with iPTH and PTH CAP. Urine calcium/creatinine ratio correlated positively with vitamin D levels.

Conclusion: In post-menopausal women with refractory osteoporosis, patients with mild renal impairment had higher phosphorus, PTH CIP, and NTX levels and lower urinary calcium. Apart from negative correlation with iPTH and PTH CAP, UCaE did not correlate with bone formation or resorption markers. Higher vitamin D levels were associated with increased urinary calcium/creatinine ratio.

Introduction

Almost every human cell relies on calcium to function properly. The synchronization of skeleton turnover, gut absorption, and renal re-absorption/excretion preserves calcium homeostasis. Interacting agents such as vitamin D, parathyroid hormone (PTH), and receptors such as PTH receptors (PTHR), vitamin D receptors (VDR), and calcium-sensing receptors (CaSR) control this homeostasis [1]. The calcium balance and bone activity should be reflected in urinary calcium excretion (UCaE) [2].

Bone is an exceptionally dynamic organ with constant regeneration caused by the coordinated action of bone cells. Through periodic replacement of old bone with newly formed bone; known as remodeling or turnover, the process of bone regeneration continues. In order to maintain physiologic remodeling and mineral hemostasis,

bone formation and resorption must be in equilibrium. When bone growth and resorption are not coupled, osteoporosis frequently results [3]. The decline in bone mass and strength leads to osteoporosis, which is a prevalent, silent illness that causes patients' impediments, lowers their quality of life, and burdens them with morbidities and mortalities [4].

The primary systemic hormones that regulate bone remodeling are thyroid hormones, PTH, vitamin D, calcitonin, glucocorticoids, sex hormones, and glucocorticoids. Many of them are mainly released for the control of serum calcium homeostasis [5].

Bone turnover markers (BTMs) play an increasingly important role in providing a dynamic assessment of bone balance (formation vs. resorption). They can assist in choosing and assessing the effectiveness of anti-osteoporotic drugs, and they can predict fracture risk independently of BMD [6]. Procollagen type-1 N-terminal propeptide (P1NP), osteocalcin, and bone-specific alkaline phosphatase (BSAP) are markers of bone formation. The C-terminal telopeptides (CTX) of type I collagen and tartrate-resistant acid phosphatase 5b (TRAP-5b) are markers of bone resorption [7, 8].

The relationship between urinary calcium excretion and bone turnover markers in patients with osteoporosis is not thoroughly studied; the current study aims to investigate this relationship.

Methods

This is a cross-sectional study of post-menopausal women who were followed up at bone clinic due to refractory osteoporosis. In accordance with the Declaration of Helsinki, the study was carried out. The Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB) examined and approved the study with the code number MD.20.12.390.

Exclusion criteria:

1. kidney disease that has reached the end stage or recent or prior organ transplantation.

2. Liver illness or liver failure.

3. Current infection, such as HIV.

4. Active cancer

5. People who have secondary causes of osteoporosis, such as Paget's disease, primary hyperparathyroidism, people taking steroids, Cushing's disease, anorexia nervosa and bulimia, active rheumatoid arthritis, malabsorption syndromes like celiac disease, inflammatory bowel disease, multiple sclerosis, and hyperthyroidism.

6. Metabolic diseases such as sarcoidosis and Fanconi syndrome that might significantly affect the UCaE were eliminated.

The medical records of the patients were examined to get demographic, clinical information, special habits, exercise, and medication use. The subsequent laboratory variables were collected:
Serum bone turnover indicators (BTMs), osteocalcin, Bone-specific alkaline phosphatase (BSAP) (ug/L), and Serum N-telopeptide Collagen (NTX). Serum creatinine, calcium, phosphorus, albumin, PTH, 25-OH-vitamin D levels, and alkaline phosphatase (nM BCE) and 24-hour urine calcium excretion.

Methods of Biochemical measurement:

Blood samples were taken in the morning after overnight fasting. Urine collection was done while patients were maintained on their regular diet.

PTH and Vitamin D:
Serum iPTH levels were determined using a radioimmunoassay (Intact PTH; Scantibodies, Santee, CA, USA); the normal range is 14–66 pg/mL; the intra-assay coefficients of variation were 5% and the inter-assay variation coefficient was 7%, and additional measurements included cyclase activating PTH (CAP); reference range 5–39 pg/ml), cyclase inhibitory PTH (CIP), and the CAP/CIP ratio.
Tandem liquid chromatography-mass spectrometry was used to measure the levels of serum 25-hydroxy vitamin D, with a normal range of 30-80 ng/mL, intra-assay coefficients of variation of 13%, and inter-assay variation coefficient of 14%. (API 3200; AB SCIEX, Framingham, MA, USA).

Bone turnover markers (BTMs):
Serum N-telopeptide Collagen (NTX) (nM BCE) was obtained as a bone resorption marker and serum osteocalcin and bone-specific alkaline phosphatase (ug/L) were collected as measures of bone production and turnover, respectively.
Serum osteocalcin was measured by an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Normal blood levels of osteocalcin vary from 11 to 46 ng/mL, with 1.4 to 4% intra-assay variability. The serum level of BSAP was measured using an enzyme immunoassay (EIA) of Metra BAP from Quidel in San Diego, California, in the United States. The range of normal serum concentrations is 18 to 75 U/L, and there is a 6% and 8% intra- and inter-assay variation, respectively. Serum NTX levels were assessed by Osteomark® Competitive-Inhibition EIA (Alere Medical, Tokyo, Japan).

Statistical analyses:

Quantitative values were expressed as mean ± standard deviation (SD) or median and range when normally or not normally distributed, respectively. Shapiro-Wilk test was used to test the data normality. Qualitative data were shown in frequency and percentages. To correlate continuous parametric data Pearson correlation was utilized while Spearman Rho correlation was applied to correlate non-parametric variables. For the above-stated statistical tests, the results were deemed significant when the error probability is ≤ 5% ($p \leq 0.05$). SPSS version 28 (IBM Corp., Armonk, NY, USA) for windows was used for data analysis and chart building.

Results

The study included 205 post-menopausal women with refractory osteoporosis. The mean age was 64 ± 10 years. The vast majority of patients were Caucasian (96%) and non-smokers (88%). HTN was found in 36%, while DM in 6%, and 13% of patients had CKD. History of kidney stones was recorded in 7%, while 77% of patients had a history of fragility fractures. ACEIs were the most used anti-hypertensive medications by the study cohort (17%), followed by beta-blockers (12%), thiazides (11%), and calcium channel blockers (9%). Nutritional vitamin D was used by the majority of patients (81%) while 52% of patients used calcium supplements. The most used anti-osteoporotic medications were bisphosphonates (67%), followed by teriparatide; which was used by 11% of patients. About one-third of patients (30.2%) were not receiving anti-resorptives or osteo-anabolics. Table 1 shows the characteristics and medication usage by the study group.

Serum calcium, total and ionized, and phosphorus levels were within the normal ranges in the majority of patients. The median vitamin D level was 38 ng/mL. Only 4% of patients had vitamin D deficiency (level < 20 ng/mL). The median iPTH was 34 pg/mL, while the serum levels of PTH CAP and CIP were 22 pg/mL and 20 pg/mL respectively. The vast majority of patients had normal kidney function with a mean serum creatinine of 0.82 mg/dl and eGFR of 83 ml/min/1.73 m^2. The laboratory characteristics of the study cohort are shown in Table 2.

Both ionized calcium and serum phosphorus correlated positively with osteocalcin (rho 0.330, 0.251, p=0.001, <0.001, respectively). Ionized calcium correlated also with NTX (rho 0.229, p=0.024). Alkaline phosphatase showed a strong positive correlation with the BSAP (rho 0.750, p<0.001) (Figure 1), a weaker correlation with

osteocalcin (rho 0.314, p=0.003), and no significant correlation with NTX (rho 0.187, p=0.081). There was a positive correlation between BSAP, NTX, and osteocalcin (rho 0.441 to 0.655, p<0.001), while only osteocalcin correlated positively with PTH (rho 0.238, 0.004 for iPTH, and rho 0.578, <0.001 for PTH CAP).

Estimated GFR correlated negatively with age (-0.446, <0.001), serum phosphorus (-0.150, 0.037), PTH CIP (-0.781, 0.002), and NTX (-0.165, 0.023). There was a positive correlation between eGFR and 24-hour urinary calcium (rho 0.264, p<0.001) (Figure 2).

Apart from PTH, 24-hour urinary calcium did not correlate with bone formation or resorption markers. PTH correlated negatively with UCaE. This was significant when PTH was measured as iPTH or PTH CAP (rho -0.366, -0.397, p<0.001, =0.005, respectively) (Figure 3 and Figure 4). Urine calcium/creatinine ratio showed the same negative correlation with PTH (rho -0.375, p<0.001), and PTH CAP (rho -0.490, p<0.001). Moreover, it showed a positive correlation with vitamin D levels (rho 0.164, p= 0.031). The correlations between UCaE and continuous variables are shown in Table 3.

Discussion:

In a study cohort of 205 post-menopausal women with refractory osteoporosis, serum calcium and phosphorus correlated positively with osteocalcin levels. Alkaline phosphatase correlated with bone formation markers; BSAP and osteocalcin. Reduction in GFR was associated with higher age, serum phosphorus, PTH CIP, and serum NTX levels, while it was associated with lower urinary calcium excretion. Apart from the negative correlation with iPTH and PTH CAP, urinary calcium did not correlate with bone formation or resorption markers. Urine calcium/creatinine ratio showed a positive correlation with vitamin D levels.

Our patients' mean age was 64 reflecting the well-known osteoporosis distribution [9]. The low frequency of comorbidities among study participants and the elimination of secondary causes of osteoporosis allowed for a better study of the relationship between urinary calcium and bone markers.

The majority of patients were receiving nutritional vitamin D and/or calcium supplements and most of them received anti-resorptive medications. This is in line with the current guidelines which recommended initial treatment of post-menopausal osteoporosis with bisphosphonates [10].

The two primary micronutrients that make up hydroxyapatite, a bone mineral that increases the organic matrix's mechanical resistance, are calcium and inorganic phosphate. About 99% and 80% of the human body's total content of calcium and phosphorus, respectively, are present in bone [11]. This could explain the observed positive correlation of ionized calcium and serum phosphorus with the bone formation marker, osteocalcin, and the bone resorption marker, NTX. Moreover, it was reported that BTMs, which reflect bone metabolism, respond to variations in the levels of bone-related nutrients such as calcium and phosphate [12].

Bone-specific alkaline phosphatase (BSAP) represents the bone-specific isoform of alkaline phosphatase; this explains the strong positive correlation between them. In most cases, alkaline phosphatase could provide appropriate clinical information in comparison to BSAP [13]. Moreover, alkaline phosphatase correlated with osteocalcin as a bone formation marker, but it did not correlate with the bone resorption marker, NTX. In resource-limited areas, alkaline phosphatase might give a hint about bone turnover status, especially bone formation activities.

There was a positive correlation between bone formation and resorption markers; this is expected because bone formation and resorption are usually coupled [14]. Osteocalcin correlated positively with PTH. Jiang et al. showed the stimulatory action of PTH on osteocalcin genes, PTH increased mRNA levels of osteocalcin in bone cells [15].

It is clear from the current study that patients with CKD were older and had higher PTH levels. eGFR and UCaE showed a favorable correlation in the entire research population of participants. This is consistent with a recently released study by Liu and colleagues on CKD patients who are not on dialysis [16]. Calcium excretion

capability is decreased in patients with renal impairment. This might be explained by the direct connection between decreased filtered load and nephron loss and decreased GFR.

The observed negative correlation between kidney function and serum phosphorus was in harmony with the known role of the kidney in phosphorus homeostasis [17]. Interestingly, we observed that the cyclase inactive PTH (CIP) increased with the reduction of kidney function. The PTH CIP is the inactive fragment 7-84 PTH [18]. The majority of our patients had normal kidney function. This increase in PTH CIP with mild renal impairment could explain the observed high prevalence of low bone turnover among patients with early CKD [19]. We noted a negative correlation between kidney function and serum NTX. It was reported that NTX is cleared by the kidneys and it is expected to be elevated in patients with renal impairment [20].

In our cohort, apart from the negative correlation with iPTH and PTH CAP, urinary calcium did not correlate with bone formation or resorption markers. It was reported that hyperparathyroidism was usually associated with an increase in urinary calcium excretion secondary to an increase in serum calcium [21]. The median PTH in our patients was 34 pg/mL, in addition, patients with primary hyperparathyroidism, as a cause of secondary osteoporosis, were excluded from the study. The negative association in our study represents the known physiological role of PTH conserving urinary calcium rather than a pathological effect of elevated PTH [22].

Urine calcium/creatinine ratio showed a positive correlation with vitamin D levels in our cohort. Leaf et al, showed that among patients with stone kidney disease and vitamin D deficiency, even limited doses of vitamin D could increase urine calcium among some patients [23]. Rathod et al, reported that urinary calcium was associated with vitamin D levels in men only [24]. Our observation extends this association to women with post-menopausal osteoporosis and highlights the importance of following vitamin D serum levels, especially in patients with a higher risk of kidney stones.

The study had some interesting results in a good number of patients and non-well-examined area, however, it was limited by its cross-sectional design.

Conclusion:

In a cohort of postmenopausal women with refractory osteoporosis, patients with mild renal impairment had higher phosphorus, PTH CIP, and NTX levels and lower urinary calcium. Serum calcium and phosphorus levels correlated with markers of bone formation and resorption. Alkaline phosphatase showed a positive correlation with bone formation markers. Apart from the negative correlation with PTH, 24-hour urinary calcium did not correlate with bone formation or resorption markers. Higher vitamin D levels were associated with increased urinary calcium/creatinine ratio.

Conflict of interest: None

Figure Legends:

Figure 1: Correlation between total and bone-specific alkaline phosphatase:

Figure 2: Correlation between GFR and 24-hour urinary calcium excretion:

Figure 3: Correlation between iPTH and 24-hour urinary calcium excretion:

Figure 4: Correlation between PTH CAP and 24-hour urinary calcium excretion:

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Table 1: Characteristics and medication usage of study group:

			N=205
Cohort Characteristics	Age		63.83 ± 10.00
	Race	Caucasian	197 (96.1%)
		African American	7 (3.4%)
		Hispanic	1 (0.5%)
	Smoking	No	172 (88.2%)
		Yes	23 (11.8%)
	Exercise	No	53 (29.4%)
		Yes	127 (70.6%)
	Hypertension		74 (36.1%)
	Diabetes		6 (3.0%)
	Coronary artery disease		14 (6.8%)
	Chronic kidney disease		26 (12.7%)
	Stone kidney disease		15 (7.3%)
	History of fragility fractures		158 (77.1%)
Medications	Diuretics		19 (9.3%)
	Beta blockers		25 (12.2%)
	ACEI		35 (17.1%)
	ARBs		10 (4.9%)
	Calcium channel blockers		19 (9.3%)
	Thiazide		22 (10.7%)
	Frusemide		11 (5.4%)
	Anti-resorptive medications		141 (68.8%)
	Osteo-anabolic medications		22 (10.7%)
	Nutritional Vitamin D		166 (81.0%)
	Calcium supplements		106 (51.7%)

Table 2: Laboratory parameters of the study cohort:

Laboratory parameters	**Study cohort**	**Normal range**
Total calcium (mg/dL)	9.60 ± 0.43	8.5 - 10.2 mg/dL
Serum phosphorus (mg/dL)	3.44 ± 0.55	2.8 - 4.5 mg/dL

Serum sodium (mEq/L)	139.9 ± 3.1	135 - 145 mEq/L
Ionized calcium (mg/dL)	5.02 ± 0.24	4.8 - 5.6 mg/dL
Urine calcium/creatinine ratio	0.18 (0.04 - 0.62)	<0.2
24-hour UCaE (mg/day)	188 (27.0 - 597)	100 - 250 mg/d
Serum creatinine (mg/dL)	0.82 ± 0.27	0.59 - 1.04 mg/dL
eGFR (ml/min/1.73 m^2)	83.35 ± 17.24	90-120 mL/min/1.73 m^2
Blood urea nitrogen (mg/dL)	14 (10 - 42)	6 - 24 mg/dL
Serum albumin (g/dL)	3.87 ± 0.30	3.4 - 5.4 g/dL
PTH (pg/mL)	34 (4 - 201)	10 - 55 pg/mL
PTH CAP (pg/mL)	22 (8 - 131)	5–39 pg/mL
PTH CIP (pg/mL)	20 (6 - 33)	
Serum vitamin D (ng/mL)	38 (10 - 100)	20 - 40 ng/mL
Alkaline phosphatase (IU/L)	66 (34 - 297)	44 - 147 IU/L
Osteocalcin (ng/mL)	20 (4 - 110)	11.3 - 18.5 ng/mL
Bone specific alkaline phosphatase (ug/L)	12.4 (6 - 45)	4.5 - 16.9 µg/L
N-telopeptide Collagen (nM BCE)	13.6 (5 - 38)	6.2 - 19 nM BCE

Data are expressed as Mean ± SD or Median (Minimum-Maximum). CAP: cyclase activating PTH, CIP: cyclase inhibitory PTH, BSAP: Bone-specific alkaline phosphatase, NTX: N-telopeptide Collagen.

Table 3: Correlations between UCaE and continuous variables:

	UCaE	
	Rho	**p-value**
Age (years)	-0.197	0.006
Weight (lbs)	0.047	0.524
Total calcium (mg/dl)	0.187	0.010
Serum phosphorus (mg/dL)	-0.089	0.223
Serum sodium (mEq/L)	0.001	0.985
Ionized calcium (mg/dL)	0.196	0.055
Urine calcium/creatinine ratio	0.877	<0.001
Serum creatinine (mg/dL)	-0.233	0.001
eGFR (ml/min/1.73 m^2)	0.264	<0.001
Blood urea nitrogen (mg/dL)	-0.051	0.492

Serum albumin (g/dL)	0.104	0.157
iPTH (pg/mL)	-0.366	<0.001
PTH CAP (pg/mL)	-0.397	0.005
PTH CIP (pg/mL)	-0.484	0.094
Serum vitamin D (ng/mL)	0.104	0.160
Alkaline phosphatase (IU/L)	0.004	0.970
Osteocalcin (ng/mL)	-0.003	0.969
Bone specific alkaline phosphatase (ug/L)	0.012	0.871
N-telopeptide Collagen (nM BCE)	-0.075	0.306

CAP: cyclase activating PTH, CIP: cyclase inhibitory PTH.

Figure 1: Correlation between total and bone specific alkaline phosphatase:

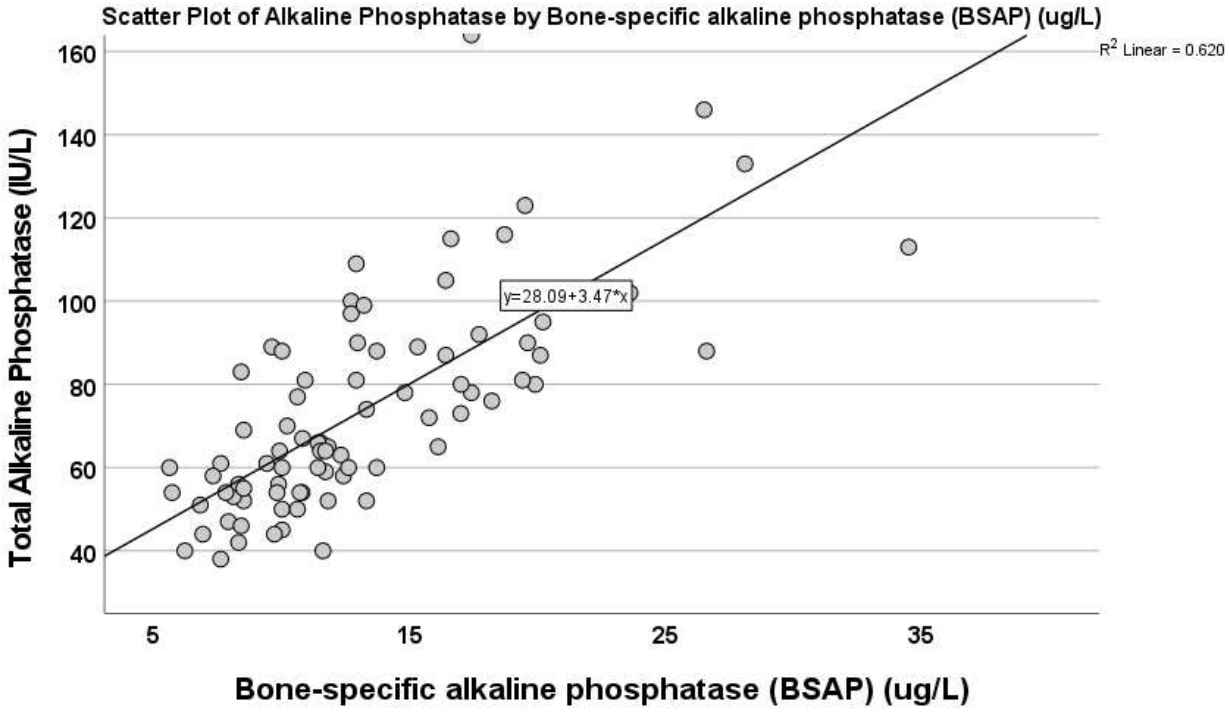

Figure 2: Correlation between GFR and 24-hour urinary calcium excretion:

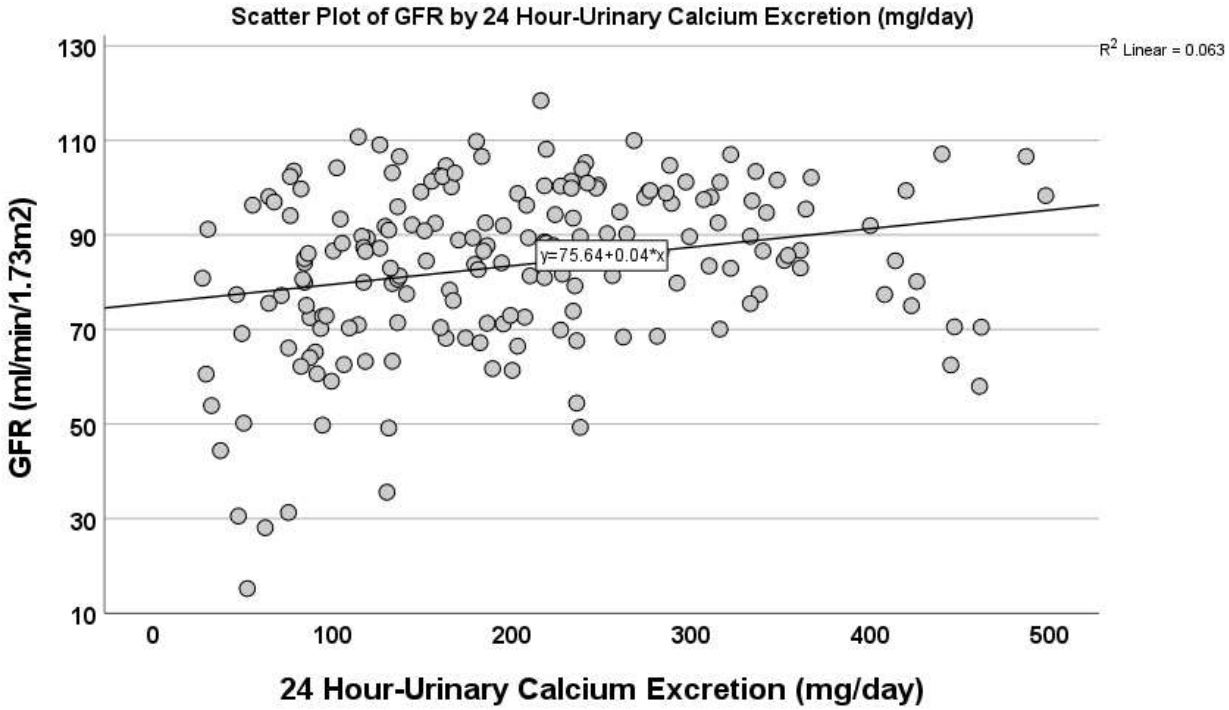

Figure 3: Correlation between iPTH and 24-hour urinary calcium excretion:

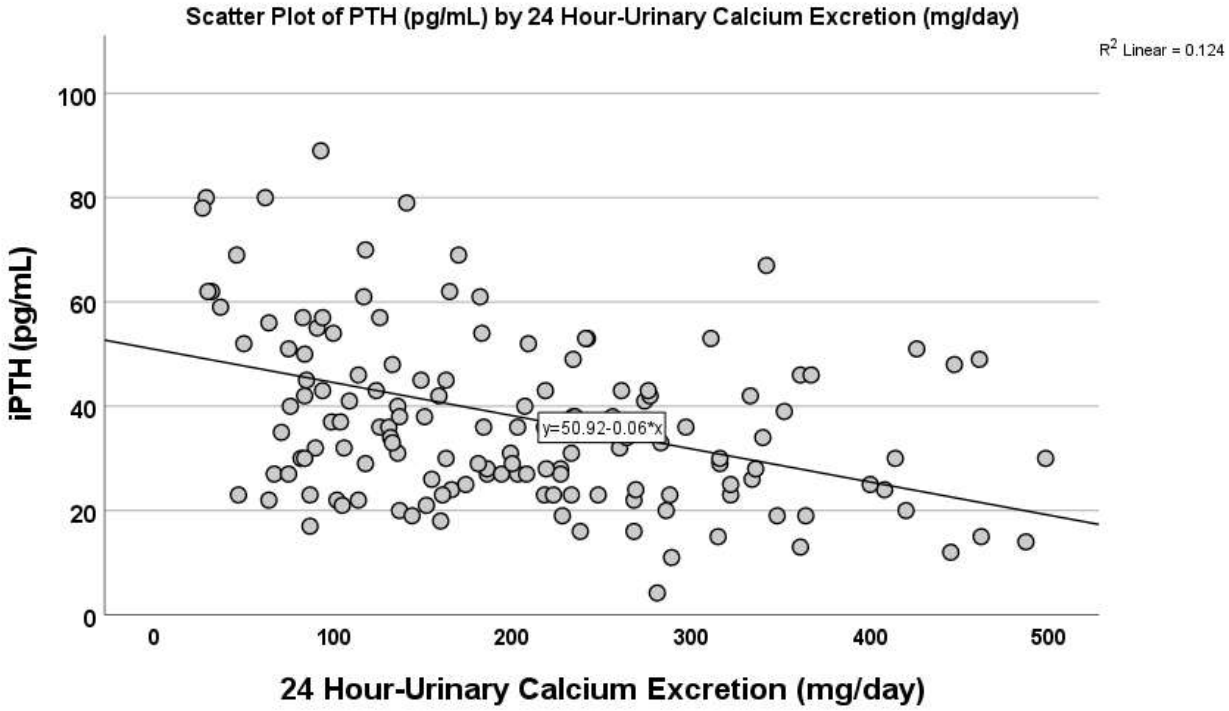

Figure 4: Correlation between PTH CAP and 24-hour urinary calcium excretion: