Serum osteocalcin level in end-stage renal disease patients on maintenance hemodialysis after parathyroidectomy in relation to parathyroid hormone level

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Background
Parathyroidectomy (PTX) is an effective treatment for refractory hyperparathyroidism in end-stage renal disease (ESRD) patients on maintenance hemodialysis (MHD). However, adynamic bone disease, a possible complication, is associated with persistent bone pain and increased fracture risk. Osteocalcin (OC) is a bone formation marker, produced by osteoblasts, stimulated by parathyroid hormone and active vitamin D, associated with overall survival. Late changes in its level after PTX need to be evaluated.
Aim
The aim of this study was to determine serum OC and its relation to intact parathyroid hormone (iPTH) in patients on MHD with and without a history of PTX.
Patients and methods
This case–control study was conducted on 50 patients with ESRD on MHD, subdivided into two groups (group I and group II), according to the history of PTX. Patients having diabetic mellitus or autoimmune disease were excluded. Patients were inquired about manifestations of bone disease. Serum concentrations of ionized total calcium, magnesium, phosphorus, alkaline phosphatase (ALP), iPTH, and OC (by ELISA) were determined. Serum OC concentration was also measured in the samples of 20 healthy participants (group III) to evaluate its reference value.
Results
Bone fracture was present in nine patients with or without PTX, with no significant difference from the other patients, as regards the studied parameters. Patients with ESRD on MHD had a significantly higher serum OC level than controls ($P<0.001$). Serum OC in patients who underwent PTX, and with adynamic bone disease (iPTH<150 pg/ml) (group IA), was significantly lower than that in the corresponding subgroup without PTX (group 2A) ($P=0.001$); similarly, the two subgroups were different, as regards serum ALP ($P<0.001$) and serum iPTH ($P<0.001$). There were significant positive correlations between serum OC and total ALP and iPTH in the total patient sample ($P<0.001$ and <0.001, respectively).
Conclusion
Adynamic bone disease after PTX in patients on MHD in comparison with those who have not undergone PTX is associated with a lower level of bone formation marker OC.

Keywords:
end-stage renal disease, maintenance hemodialysis, osteocalcin, parathyroid hormone, parathyroidectomy

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Introduction

Osteocalcin (OC) is an osteoblast-secreted protein. OC, a bone formation marker, is negatively correlated with abdominal aortic calcification progression and positively with overall survival [1,2].

Chronic kidney disease (CKD)-mineral bone disease (MBD) is characterized by the following (and they are): (i) abnormal metabolism of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D; (ii) bone abnormalities and (iii) soft-tissue calcifications [3].

Parathyroidectomy (PTX) is an effective treatment for secondary hyperparathyroidism in CKD-MBD patients. Up to 90% of patients who underwent PTX had adynamic bone disease [4,5].

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This study aimed to assess post-PTX level of serum OC and its relation to intact parathyroid hormone (iPTH) in patients on maintenance hemodialysis (MHD).

Patients and methods

Patients

A case–control study was conducted on adult patients with end-stage renal disease (ESRD) on MHD who were selected from three outpatient dialysis units (Moassa Dialysis Unit Alexandria University, Dialysis Units of Fever Hospital and Aboukir Hospital of Ministry of Health, Alexandria, Egypt). After informed consent and local ethical committee approval, the patients were recruited for the study; the practical work has been carried out in accordance with the code of Ethics of the World Medical Association (1964 Declaration of Helsinki and its later amendments).

This study included 50 patients on MHD with a duration that varied from 3 to 18 years, three times weekly, 4 h/session, using high-flux dialyzer for MHD on the first and last day of the week for at least 1 year before recruitment for the study. A Fresenius machine was used.

Patients were subdivided into the following (and they are):

Group I: 20 patients on MHD for whom PTX was performed since 1–7 years (the time of performing the study) were subclassified according to PTH level after operation into group IA including 12 patients with adynamic bone disease (PTH<150 pg/ml [6,7]), patients with persistent hyperparathyroidism having a (group IB) PTH level more than 300 pg/ml [6,7] (five of them had iPTH>600 pg/ml). One patient who had serum iPTH level within the accepted range (PTH>150 to <300 pg/ml) was excluded from statistical analysis (not included in the subgroups).
Group II: group IIA comprised 15 patients on MHD with adynamic bone disease (PTH level<150 pg/ml). Group IIB comprised 15 patients on MHD with hyperparathyroidism (PTH>300 pg/ml).
20 healthy nondiabetic and nonobese participants with normal renal function were also included (group III).
Exclusion criteria: patients with a history diabetes mellitus, autoimmune disease, that is, Systemic Lupus Erythematosus (SLE) or active hepatic disease, and pregnant female individuals were excluded.

All patients submitted to complete history taking and clinical examination, with emphasis on complaints related to bone disease.

Laboratory investigations

All patients underwent routine investigations including complete blood count (CBC), liver enzymes, blood urea nitrogen (BUN) and serum creatinine, and serum level of total ionized calcium, magnesium, and phosphorus, serum alkaline phosphatase (ALP), serum iPTH, and serum OC. Blood samples for PTH level were taken at the time of taking samples for determination of OC.

Serum OC was measured by ELISA in hemodialysis patients and in 20 healthy participants with normal renal functions (group III).

For determination of serum OC in the patients, blood samples were collected before the first session of the week, samples were immediately centrifuged and the serum was frozen at less than −20°C until determination; the determination was carried out at not more than 3 weeks of sample collection. OC was measured by ELISA (Epitope Diagnostics Inc., San Diego, California, USA).

Data management

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (IBM Corp., Armonk, New York, USA) [8]. Qualitative data were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, SD and median. χ^2-Test was used for categorical variables, to compare between different groups, and Fisher's exact or Monte Carlo correction was used for χ^2 when more than 20% of the cells had an expected count less than 5; the Student t-test was used for normally distributed quantitative variables, to compare between two studied groups. The Mann–Whitney test was used for abnormally distributed quantitative variables, to compare between two studied groups. The Kruskal–Wallis test was used for abnormally distributed variables to compare more than two groups. Significance of the obtained results was judged at the 5% level. Correlation analysis was carried out when appropriate.

Results

This study included 50 patients with ESRD on MHD. History of generalized bone pain was found in 33 patients, and 14 of them underwent PTX. Pelvic

and bone fracture was found only in nine patients (four of them underwent PTX).

One male patient with a history of PTX had a serum iPTH level of 300 pg/ml (accepted range of iPTH 150–300 pg/ml) and serum OC level of 188.017 ng/ml was excluded from the statistics (not included in subgroups).

Table 1 shows the demographic data in patients and controls; statistically no significant difference was found between patients and controls as regards sex and age ($P>0.05$).

Patients with and without PTX had a statistically significant increase in OC level in comparison with controls ($P\leq0.001$ and <0.001, respectively; Table 2).

Table 3 shows the comparison between patient subgroups, adynamic bone disease and hyperparathyroidism patients, with or without PTX, as regards routine investigations such as those of ionized, total calcium, magnesium, hemoglobin (Hb) and phosphorus; statistically, there was no significant difference between the four subgroups, as regards pervious parameters.

There was a significant difference between subgroups with adynamic bone disease who underwent PTX (group IA) and those with adynamic bone disease without undergoing PTX (group IIA) as regards OC (mean ±SD=112±68 vs. 212.5±59 ng/ml, respectively, $P=0.001$; Table 4); moreover, there was a significant difference between each subgroup and the control group wherein the OC level was lower in the control group than in the subgroups (Table 4). In addition, serum concentration of ALP and iPTH was significantly lower in group IA in comparison with group IB (Table 5).

In contrast, no significant difference was noticed between the two subgroups with hyperparathyroidism, with or without PTX, as regards previously mentioned parameters.

Table 6 compares the different parameters of patients on MHD with (nine patients) and without (40 patients) history of bone fracture. No significant difference was found as regards age, sex, OC, ALP, PTH, ionized, total calcium, magnesium and Hb. Bone fracture was found in both group I and group II.

A significant positive correlation between serum OC and serum ALP and serum iPTH ($r=0.64$, 0.48 and $P<0.001$, <0.001, respectively) in the patients with ESRD on MHD was noticed (Fig. 1).

Moreover, a significant positive correlation between serum PTH and serum ALP ($r=0.628$ and $P<0.001$) in the ESRD patients on MHD was noticed (Fig. 2).

Table 1 Demographic data: comparison between patient groups according to history of parathyroidectomy or not and controls as regards sex and age (*N*=69)

	Parathyroidectomy	No parathyroidectomy	Controls	Total	Test
N (%)	19 (27.5)	30 (43.6)	20 (28.9)	69 (100.0)	
Sex [*N* (%)]					
Male individuals	10 (52.6)	13 (43.3)	8 (40.0)	31 (44.9)	χ^2-Test $\chi^2=0.683$ $P=0.711$
Female individuals	9 (47.4)	17 (56.7)	12 (60.0)	38 (55.1)	
Total	19 (100.0)	30 (100.0)	20 (100.0)	69 (100.0)	
Age					
Mean±SD	47±12.4	44.4±12.1	38.5±12.4	43.4±12.5	Kruskal–Wallis test $\chi^2=4.821$ $P=0.09$
Median	43	44.5	36	43	
Minimum–maximum	30–70	24–68	23–60	23–70	

Table 2 Comparison between patient groups according to history of parathyroidectomy or not and controls as regards osteocalcin (*N*=69)

	Parathyroidectomy	No parathyroidectomy	Controls	Total	Kruskal–Wallis test
N (%)	19 (27.5)	30 (43.6)	20 (28.9)	69 (100.0)	
Osteocalcin					
Mean±SD	161.8±97.2*,†	241.8±68.9‡	64.8±21.2	168.5±100.9	$\chi^2=35.465$ $P\leq0.001$
Median	137.7	256.8	66.5	141.4	
Minimum–maximum	61.3–318.0	46.0–318.2	10.2–102.3	10.2–318.2	

*$P=0.012$ when compare with no parathyroidectomy group. †$P<0.001$ when compared with controls. ‡$P<0.001$when compared with controls.

Table 3 Distribution of biochemical parameters in end-stage renal disease patients according to hemoglobin level and serum concentration of ionized total calcium, magnesium and phosphorus (*N*=49)

Parameters	Parathyroidectomy adynamic (group IA)	Parathyroidectomy hyperparathyroidism (group IB)	Adynamic (group IIA)	Hyperparathyroidism (group IIB)	Kruskal–Wallis test (*P* value)
N (%)	12 (17.4)	7 (10.1)	15 (21.8)	15 (21.8)	
Ionized calcium (mg/dl)					
Mean±SD	4±0.8	3.9±0.8	4.6±0.5	4.3±0.7	χ^2=7.3 *P*=0.06
Median	4	3.8	4.6	4.3	
Minimum–maximum	2.6–5.2	2.8–5.4	3.8–5.3	3.2–5.7	
Total calcium (mg/dl)					
Mean±SD	8.4±1.0	8.4±1.0	8.0±1.2	8.4±1.0	χ^2=1.509 *P*=0.680
Median	8.5	8.7	8	8.7	
Minimum–maximum	6.3–10.1	6.4–9.5	5.1–9.9	6.4–9.5	
Mg (mEq/l)					
Mean±SD	2.3±0.3	2.2±0.3	2.3±0.3	2.4±0.3	χ^2=3.1 *P*=0.37
Median	2.2	2.1	2.1	2.4	
Minimum–maximum	1.7–2.8	1.9–2.5	1.9–2.9	1.7–2.9	
Hb (g/dl)					
Mean±SD	8.5±2.1	10.4±2.4	9.9±1.6	9.9±1.2	χ^2=7.7 *P*=0.053
Median	8	10.6	10.1	10	
Minimum–maximum	5.2–13.7	7–14	7.2–12.5	8.5–12.2	
Phosphorus (mg/dl)					
Mean±SD	5.6±2.2	4.87±1.4	5.3±1.7	4.98±10.5	χ^2=0.246 *P*=0.970
Median	5.7	4.6	5	5	
Minimum–maximum	2.3–8.9	3–7.2	2.9–8.4	2.8–8.4	

Hb, hemoglobin;

Table 4 Comparison between subgroups in all patients and controls as regards osteocalcin (*N*=69)

Parameter	Parathyroidectomy adynamic group IA	Parathyroidectomy hyperparathyroidism group IB	Adynamic group IIA	Hyperparathyroidectomy group IIB	Control group III	Kruskal–Wallis test (*P* value)
N (%)	12 (17.4)	7 (10.1)	15 (21.8)	15 (21.8)	20 (28.9)	
Osteocalcin (ng/ml)						
Mean±SD	112±68*,†,‡,§	246.9±80.5$^{\|\|}$	212±59¶,**	271.5±66.9††,‡‡	64.9±21.2	χ^2=44.5 *P*≤0.001
Median	81.88	293.2	246.6	293.2	66.5	
Minimum–maximum	61–305	101.6–318.0	102.4–281.8	46–318.2	10.2–102.3	

$^{*}P$=0.006 when compared with group IB. $^{\dagger}P$=0.001 when compared with group IIA. $^{\ddagger}P$=0.001 when compared with group IIB. $^{\S}P$=0.01 when compared with group III. $^{\|\|}P\leq$0.001 when compare with group III. $^{\P}P$=0.001 when compared with group IA. $^{**}P$=0.002 when compared with group IIB. $^{\dagger\dagger}P\leq$0.001 when compared with group III. $^{\ddagger\ddagger}P$=0.002 when compared with group IIA.

Discussion

The first biomarker used for biochemical assessment of bone turnover was PTH. Most studies conducted in the 1980s and early 1990s demonstrated a relatively good correlation between levels of PTH and bone histomorphometric parameters [9].

The 2003 National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines [6] recommend a PTH target of 150–300 pg/ml. The guidelines proposed by the Kidney Disease Outcomes Quality Initiative suggested that an iPTH level greater than 300 pg/ml for high turnover presented a positive predictive value of 62%, but the 2009 KDIGO Guidelines [7] suggested maintaining iPTH levels for patients with CKD stage 5D between two and nine times the upper limit of normal for the assay. According to this, hyperparathyroidism (HPT) is considered if PTH is more than 600 pg/ml.

In this study, patients with ESRD were considered to suffer from adynamic bone disease if the serum PTH level was less than 150 pg/ml [10].

Table 5 Comparison between maintenance hemodialysis patients with or without parathyroid operation as regards serum level of intact parathyroid hormone and alkaline phosphatase (*N*=49)

Parameters	Parathyroidectomy adynamic group IA	Parathyroidectomy hyperparathyroidism group IB	Adynamic group IIA	Hyperparathyroidism group IIB	Kruskal–Wallis test (*P* value)
Parathyroid hormone (pg/ml)	12 (24.5)	7 (14.3)	15 (30.6)	15 (30.6)	$P \leq 0.001$
Mean±SD	43.4±40.7*,†,‡	1501.7±1405.1$^{\S,\|\|}$	125.5 ±15.9¶,**,††	1244.2±888.46‡‡	
Median	19.95	1132	132	937	
Minimum–maximum	5–121	375–4396	97.1–145	538–3816	
Alkaline phosphatase (IU/ml)					
Mean±SD	74.3±16.7*,†,‡	234.6±316.5§	151.8 ±43.7$^{\|\|,\P}$	368.4±287**	$P \leq 0.001$
Median	71	121	140	291	
Minimum–maximum	52–109	76–944	109–258	53–1112	

$^{*}P \leq 0.001$ when compared with group IB. $^{\ddagger}P \leq 0.0012$ when compared with group IIB. $^{\dagger}P \leq 0.001$ when compared with group IIA. $^{\S}P \leq 0.001$ when compared with group IA. $^{\|\|}P \leq 0.001$ when compared with group IIA. $^{\P}P \leq 0.001$ when compared with group IA.$^{**}P \leq 0.001$ when compared with group IB. $^{\dagger\dagger}P \leq 0.001$ when compared with group IIB. $^{\ddagger\ddagger}P \leq 0.001$ when compared with group IIA.*** $P=0.010$ when compared with group IB. $^{\dagger}P \leq 0.001$ when compared with group IIA. $^{\ddagger}P \leq 0.001$ when compared with group IIB. $^{\S}P=0{\cdot}010$ when compared with group IA. $^{\|\|}P \leq 0.001$ when compared with group IA. $^{\P}P=0.006$ when compared with group IIB. $^{****}P=0.006$ when compared with group IIA.

Gal-Moscovici *et al.* [11] used bone histomorphometry and described a close correlation between PTH level, 150 pg/dl and low turnover bone disease.

Subsequently, Barreto *et al.* [12] used bone histomorphometry to show that dialysis patients with iPTH levels of 150–300 pg/ml had low-turnover bone disease, and, also, Lehmann *et al.* [13] showed that a serum PTH level of 161 pg/ml differentiated high versus low/normal bone turnover with a sensitivity of 75% and PPV of 89%.

Barreto *et al.* [12] showed that an iPTH of 300 pg/ml has a sensitivity of 69% and specificity of 75% for high turnover bone disease.

According to the previously mentioned studies, 60% (12/20) of the patients in our study who underwent PTX were considered to have adynamic bone disease, 35% (7/20) hyperparathyroidism, and only one (5%) patient had an iPTH level within the target level. Hernandes *et al.* [14] reported that 90% of patients had adynamic bone disease after PTX for secondary hyperparathyroidism.

Sixty-six percent (33/50) of the patients with ESRD in this study suffered from bone pain; meanwhile only nine patients had proven fractures (vertebral and pelvic bones). Bone fracture occurred in patients with hyperparathyroidism (five patients) and adynamic bone disease (four patients) with or without PTX.

Disturbances in mineral metabolism and bone diseases are called CKD-MBD, and they are common complications of CKD. In general, the classical osteitis fibrosa cystica (primary hyperparathyroidism) is mostly without clinical symptoms. In the case of osteitis fibrosa cystica, induced by secondary hyperparathyroidism, pain and fragility of the bone are frequent complications. Moreover, osteomalacia, caused by vitamin D deficiency, and adynamic bone disease, are often associated with pain and fractures, as shown by Ritz *et al.* [15].

Despite limited data, it seems that musculoskeletal pain is the most common of the chronic pain syndromes in ESRD, as in the general population. However, unlike in the general population [16], musculoskeletal pain in ESRD is, on average, equal in severity to neuropathic and ischemic pain. A synergistic effect of hyperparathyroidism and osteoarthritis in the development of bone pain may contribute to the high prevalence and severity of musculoskeletal pain in this population. However, the relative roles of osteoarthritis and renal osteodystrophy in these chronic pain syndromes of ESRD patients are not clear [16].

According to a study carried out by Kazama *et al.* [17], the direct cause of fragility fracture was reported to be osteoporosis.

CKD-MBD has a potential to cause osteoporosis. The frequency of falls is another major risk of fragility fracture, and uremia also increases the risk of fall due to cognitive dysfunction, osteopenia and bone material deterioration [18]. The patients in this study who suffered from bone fracture were not significantly different from the other patients as regards hemoglobin level, serum concentrations of electrolytes, iPTH, OC and ALP.

Table 6 Comparison of different parameters between all patients according to bone fracture status (*N*=49)

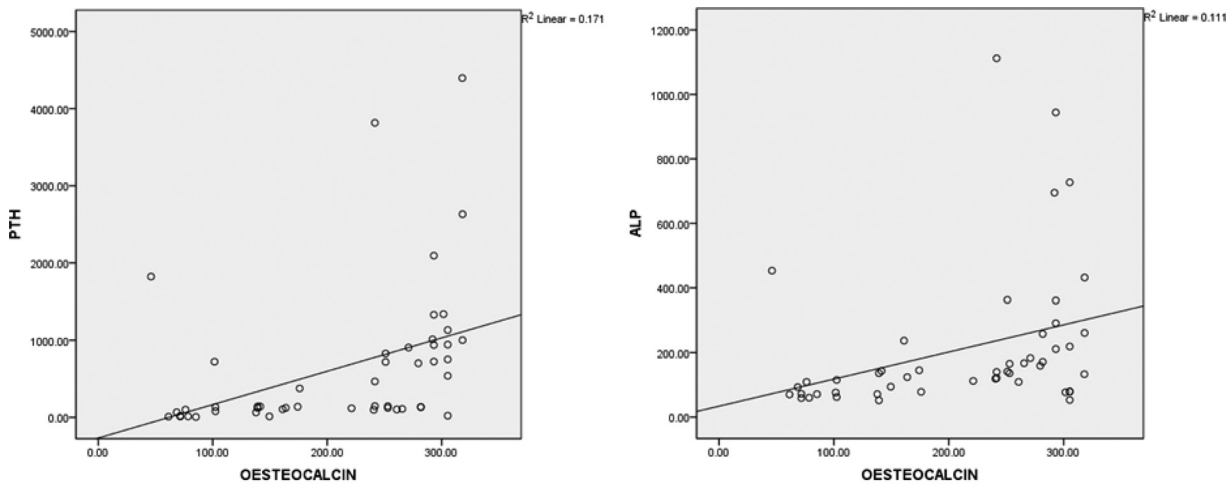
Parameters	Fracture [*N* (%)]		Test
	No (*n*=40)	Yes (*n*=9)	
N (%)	40 (81.6)	9 (18.4)	
Age (years)			
<60	33 (82.5)	9 (100)	χ^2-Test χ^2=183.8 *P*=0.175
>60	7 (17.5)	0	
Total	40 (100.0)	9 (100)	
Sex			
Males	19 (47.5)	4 (44.4)	Fisher's exact test χ^2=0.028 *P*=1.0
Females	21 (52.5)	5 (55.6)	
Total	40 (100.0)	9 (100.0)	
Parathyroid hormone (pg/ml)			
Mean±SD	644.5±994.7	644.5±932.5	Mann–Whitney test, *P* value *U*=161.0 *P*=0.633
Median	140	142.5	
Minimum–maximum	5–2631	8.8–4396	
Osteocalcin (ng/ml)			
Mean±SD	199.5±92.4	213.3±89.5	*U*=175.0 *P*=0.907
Median	161.0	246.3	
Minimum–maximum	85.2–318.2	46–318.2	
Alkaline phosphatase (IU/ml)			
Mean±SD	297.1±318	191.6±199.0	*U*=154 *P*=0.510
Median	165	128.5	
Minimum–maximum	62–944	52–1112	
Ca^{2+} (mg/dl)			
Mean±SD	4.6±0.25	4.2±0.65	*U*=146.5 *P*=0.386
Median	4.2	4.3	
Minimum–maximum	3.3–5.9	2.6–5.6	
Total calcium (mg/dl)			
Mean±SD	8.3±1.1	8.5±0.7	*U*=173.0 *P*=0.856
Median	8.5	8.6	
Minimum–maximum	5.1–10.7	7.3–9.5	
Magnesium (mEq/l)			
Mean±SD	2.4±0.25	2.3±0.32	*U*=141.5 *P*=0.362
Median	2.3	2.2	
Minimum–maximum	2.1–2.8	1.7–2.9	
Hb (g/dl)			
Mean±SD	8.9±1.3	9.8±1.8	*U*=122.5 *P*=0.137
Median	9.0	10	
Minimum–maximum	7.2–11	5.2–14	

Hb, hemoglobin;

Unlike our results, Maruyama *et al.* [19] reported that elevated serum level of ALP, a likely marker for accelerated bone metabolic activity, is associated with a higher risk of fracture incidence.

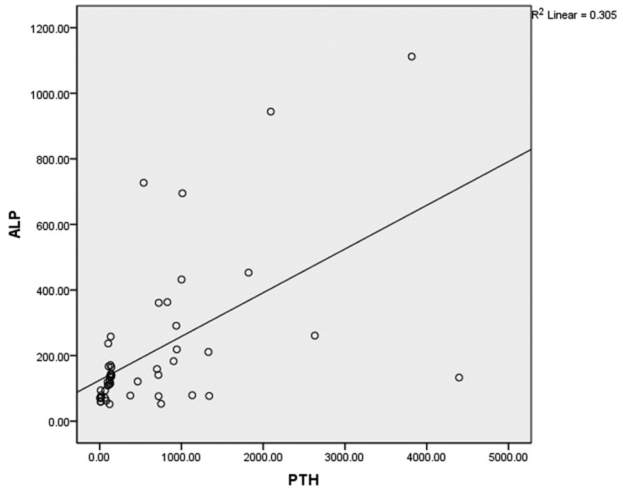
However, controversy still remains on the relationship between parathyroid function and structure-related bone strength. One possible explanation for this issue is that an extremely high plasma level of PTH is required to cause evident cortical thinning in dialysis

Figure 1



(a, b) Correlation between serum osteocalcin (ng/ml) and each of serum alkaline phosphatase (IU/l) and serum intact parathyroid hormone (pg/ml) (r=0.64, 0.48 and $P<0.001$, <0.001, respectively) in the end stage renal disease patients on maintenance hemodialysis by spearman correlation for abnormally distributed data.

Figure 2



Correlation between serum intact parathyroid hormone (pg/ml) and alkaline phosphatase (IU/l) (r=0.628, $P<0.001$) in end stage renal disease patients on maintenance hemodialysis.

patients because skeletal resistance to PTH stimuli is increased in the uremic condition [20,21].

Investigators have speculated that in the adynamic bone condition (low frequency of bone remodeling), the bone mechanical strength could be deteriorated through accumulated microdamages, Seref-Ferlengez *et al.* [22].

Other factors such as blood pressure level, medications and acid base status may contribute to fall or fracture. Kato *et al.* [23] found that the serum bicarbonate concentration has a significant relationship with fracture risk in Japanese patients with ESRD on MHD. Unfortunately, predialysis serum bicarbonate level was not investigated in this study.

In addition, the study by Hocher *et al.* [24] showed that most fragility fractures occur due to a fall.

In this study patients having PTX were subclassified to group IA (12 patients) with adynamic bone disease and group IB (seven patients) with hyperparathyroidism and serum PTH level more than 300 pg/ml (with five of them having serum iPTH level above 600 pg/ml).

As regards serum OC level, no significant difference was found among group I and group II in total, but significantly lower serum OC ($P<0.001$) was noticed in patients with adynamic bone disease having PTX (group IA), in comparison with those without PTX (group IIA).

Similarly, a lower level of serum iPTH ($P<0.001$) and ALP ($P<0.001$) was noticed in group IA in comparison with group IIA (Tables 4 and 5). In contrast, serum OC level, iPTH, and ALP were not significantly different in patients with hyperparathyroidism with or without PTX.

PTX represents a point of no return, and many patients need lifelong calcium and vitamin D to maintain normal calcium levels, which by their suppressive effect may

be contributing to a lower level of iPTH in patients with adynamic bone disease after undergoing PTX.

In this study, serum OC ranged from 10.2 to 102.4 ng/ml in healthy controls, which was higher than the reported normal range of 3.8–25.8 ng/ml [25].

This could be due to the difference in the age or adiposity of the studied sample. Kuk *et al*. [26] reported that serum OC levels were negatively correlated with age and visceral adiposity in Chinese patients; in addition, they reported that the serum OC levels were negatively correlated with all the anthropometric indices of obesity, systolic blood pressure (SBP), fasting blood sugar (FBS), 2 hour post prandial blood sugar (2hppBS), haemoglobin A1 C (Hb1c), HOMA–insulin resistance (HOMA-IR), total cholesterol (TC), triglycerides (TG), free fatty acids (FFA), C reactive protein (CRP), but positively correlated with adiponectin in diabetic obese patients. In our study, healthy nonobese participants with a mean age of 38.5±12.4 years constituted the control group.

Gerakis *et al*. [27] performed a histopathological bone study in patients with CKD on MHD, and they reported that the diagnosis of adynamic bone disease was considered if the serum PTH level was less than 65 pg/ml, and if serum OC was less than 20 ng/ml. In their study, serum OC for healthy controls ranged from 5 to 13.5 ng/ml, compared with our study, in which it was 10.2–102.4 ng/ml for healthy controls.

Aluminum bone deposition in the study by Gerakis *et al*. [27] was found in 66/144 (58%) of the total number of patients, and nine of them had adynamic bone disease.

Aluminum bone deposition and retention is recently avoided by better water quality used for hemodialysis, and, also, physicians have become more aware of not using antacids as a phosphate binder in CKD patients. This could explain the higher level of serum OC than that reported by Gerakis *et al*. [27] for the patients with adynamic bone disease in this study. Moreover, Kuzniewski *et al*. [28] reported a higher level of carboxylated OC and uncarboxylated OC in patients on MHD than in healthy controls. Loss of residual renal function, uremic situation, and chronic inflammation induced with hemodialysis may influence the OC level and explains the higher level of OC in patients than in controls in this study.

Gaur *et al*. [29] reported the important role of ALP in mineralization, by the phased expression of genes during osteoblastic differentiation and growth plate cartilage calcification. In both tissues, bone and calcifying cartilage, ALP is expressed early in development, and is soon observed on the cell surface and in matrix vesicles. Later in the developmental program, on the other hand, other genes like OC are upregulated, and ALP expression decreases. Serum total ALP was significantly lower in patients with adynamic bone disease with PTX in this study relative to those without PTX. In addition, there was a positive correlation between serum OC and serum total ALP level in the total patient sample on MHD (50 patients) in this study with or without PTX. In addition, patients in this study were selected on the basis of having no active hepatic disease to exclude its effect on the level of serum ALP. Kidney Disease Outcomes Quality Initiative guidelines recommend monitoring serum total ALP every 12 months and more frequently if PTH is elevated [30].

Conclusion

Bone fracture, in the ESRD patients on MHD, with or without PTX, in this study, is not related to age, sex, serum iPTH and serum OC.

PTX in ESRD patients on MHD in this study is not only complicated with adynamic bone disease in a great percentage of patients, but is also associated with lower level of bone formation marker OC than the corresponding patients without PTX. Serum OC is positively correlated with total ALP and serum iPTH in ESRD patients on MHD.

The limitations of this study are the relatively small number of studied participants and that it did not include a histomorphometric study of bones before or after PTX.

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There are no conflicts of interest.

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