

# The Importance of Bone Biomarkers in the Diagnosis of Renal Osteodystrophy

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## ABSTRACT

**Objective:** To evaluate the association of serum biochemical markers in patients with chronic kidney disease (CKD) in Jamaica for early detection of renal osteodystrophy (ROD).

**Methods:** The study contained two groups: CKD group (221) which consisted of adult patients, from dialysis units and renal clinics, with stage III to V CKD. The control group (237) had adult individuals, from the medical outpatient clinics, with mild and controlled chronic diseases and absence of renal failure. The patients in the study were between 18–80 years of age and gave informed consent to participate in the study. The differences in distribution of demographic, clinical and pathologic variables between the two groups were evaluated. Pearson's chi-squared test and Spearman's rho correlation coefficient test was used, with  $p < 0.01$  considered statistically significant. Data analysis was conducted using the statistical package for the social sciences (SPSS) version 17.0.

**Results:** Among the 221 CKD patients in the study, 174 (78.7%) had ROD based on serum intact parathyroid hormone (iPTH) levels. The majority of patients in the control group did not have bone disease ie 95–96%. The majority of CKD patients (70.0%) had high-turnover (HTO) bone disease compared to 29.3% of patients with low-turnover (LTO) bone disease. Dialysis patients who had HTO bone disease compared with those with LTO had significantly higher levels of iPTH and total serum alkaline phosphatase (ALP). A similar relationship was observed among CKD patients not on dialysis. There was a significant individual variation in bone turnover biochemical markers.

A total of 237 patients were recruited in the control group. Based on the levels of iPTH and tALP, six of them were found to have bone disease. The majority of these patients with bone disease were diabetic (83.3%) while the other patient had cancer (16.7%). The six patients in the control group with bone disease were within the age cohort of 64–80 years, most of whom were 78 years old.

**Conclusion:** A combination of serum biochemical markers might predict underlying renal osteodystrophy better than individual biochemical markers. A predictive model using bone histology and biochemical markers can be developed in the future.

**Keywords:** Biomarkers, chronic kidney disease, parathyroid hormone, renal osteodystrophy

## Importancia de los Biomarcadores Óseos en el Diagnóstico de la Osteodistrofia Renal

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## RESUMEN

**Objetivo:** Evaluar la asociación de marcadores bioquímicos séricos en pacientes con la enfermedad renal crónica (ERC) en Jamaica, para la detección precoz de la osteodistrofia renal (ODR).

**Métodos:** El estudio comprendió dos grupos: un grupo ERC (221) formados por pacientes adultos, provenientes de las unidades de diálisis y las clínicas renales, y en las fases III a V de la ERC. El grupo control (237) estaba constituido por individuos adultos, provenientes de las clínicas ambulatorias médicas, con enfermedades crónicas moderadas y controladas, y sin insuficiencia renal. Los pacientes del estudio tenían edad que fluctuaban de 18 a 80 años de edad y dieron consentimiento informado para participar en el estudio. Se evaluaron las diferencias en la distribución de las variables

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demográficas, clínicas y patológicas entre los dos grupos. SE usaron la prueba de chi-cuadrado de Pearson y la prueba de coeficiente de correlación rho de Spearman, considerándose  $p < 0.01$  estadísticamente significativa. El análisis de los datos se llevó a cabo usando paquete que usó el paquete estadístico para las ciencias sociales (SPSS) versión 17.0.

**Resultados:** De los 221 pacientes de ERC en el estudio, 174 (78.7%) tenían ODR, basado en los niveles de hormona paratiroidea intacta (PTHi) sérica. La mayor parte de los pacientes en el grupo de control, ie. 95–96%, no tenían enfermedades óseas. La mayoría de los pacientes con ERC (70.0%) presentaban la enfermedad de alto recambio óseo (ARO) en comparación con 29.3% de pacientes con la enfermedad de bajo recambio óseo (BRO). Los pacientes de diálisis con alto recambio óseo – comparados con los de bajo recambio óseo – tuvieron niveles significativamente más altos PTHi y fosfatasa alcalina sérica total (FAS<sub>t</sub>). Una relación similar se observó entre pacientes de ERC sin tratamiento de diálisis. Hubo una variación individual significativa en los marcadores bioquímicos de recambio óseo. Un total de 237 pacientes fueron reclutados para el grupo de control. Sobre la base de los niveles de PTHi y FAS<sub>t</sub>, se hallaron seis con la enfermedad ósea. La mayoría de estos pacientes con enfermedad ósea eran diabéticos (83.3%) mientras que el otro paciente tenía cáncer (16.7%). Los seis pacientes en el grupo de control con enfermedad ósea estaban dentro de la cohorte de 64–80 años de edad, en la que la mayoría tenía 78 años.

**Conclusión:** Una combinación de marcadores bioquímicos séricos podrían predecir una osteodistrofia renal subyacente mejor que los marcadores bioquímicos individuales. En el futuro puede desarrollarse un modelo de predicción que use marcadores tanto bioquímicos como histológicos del tejido óseo.

**Palabras claves:** Insuficiencia renal crónica, biomarcadores óseos, enfermedad ósea, osteodistrofia renal

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## INTRODUCTION

Chronic renal failure is a significant public health problem in Jamaica and is placing an increasing financial burden on the healthcare sector (1). A survey on chronic renal failure in Jamaica conducted by Barton *et al* estimated that the crude point prevalence of chronic renal failure in persons 20 years and over at the end of 1999 was 327 per million population per year (2). Chronic kidney disease (CKD) is associated with multiple complications and renal osteodystrophy (ROD) is significant among them (3). Renal osteodystrophy is associated with high morbidity and mortality (4–6), as patients with end-stage renal disease (ESRD) are at increased risk of bone loss and hip fracture (7, 8). The incidence of fracture in ESRD is reported to be 1% per year for the hip and about 2.6% for any other fracture (9, 10) although the incidence of hip fracture in the general population is only 0.07%–0.22% (11).

Renal osteodystrophy is broadly classified into: osteitis fibrosa (OF), osteomalacia (OM), adynamic bone disease (ABD) and mixed osteodystrophy [MOD] (12). Although patients with a mild to moderate degree of CKD rarely experience symptoms, these skeletal changes develop years before symptoms arise (13). As therapy for ROD varies, it is essential to establish the underlying diagnosis before assigning appropriate treatment. At present, bone biopsy is the gold standard for diagnosis of ROD; however, because of its invasive nature and overall complexity, clinicians rely on serum parathyroid hormone (PTH) levels for the diagnosis and treatment of ROD in CKD patients. Renal scan may also be employed to aid diagnosis.

The purpose of this research was to study the prevalence of and evaluate an association between serum biochemical markers such as calcium, phosphorus, PTH, total alkaline phosphatase (ALP), bone specific alkaline phosphatase (bsALP), osteocalcin (OC) or vitamin D, serum uric acid, creatinine and albumin in order to predict a diagnosis of ROD.

## SUBJECTS AND METHODS

There were two groups in the study. The CKD group consisted of adult patients with CKD stage III to V from major institutions: University Hospital of the West Indies (UHWI) haemodialysis and peritoneal dialysis units, Diabetic Association Renal Unit (DARU) St Joseph's Hospital (SJH) haemodialysis units as well as the Mandeville Regional Hospital (MRH) renal outpatient clinic. A control group of adult individuals with no known renal failure were recruited from the medical outpatient clinics from UHWI, MRH and St Ann's Bay hospital (SABH). The comparison group, had mild and controlled chronic diseases but no renal disease. The patients in the study were between 18–80 years of age and had obtained informed consent. The study was approved by the Ethics Committee, Faculty of Medical Sciences, at the University of the West Indies (UWI) and the University Hospital of the West Indies.

Using the Sample Power statistical software, set at type 1 error (alpha) = 0.05 and power of 90%, the minimum number of participants needed to pick up a mean difference from normal was calculated to be six persons per group of interest. The groups of interest included analyses broken

down by six age categories, two gender categories, four body mass index (BMI) categories, and two overall grouping of cases *versus* controls. Hence a minimum of 480 participants (240 cases with renal failure and 240 comparison subjects without kidney disease) were needed for this study. Cases and control patients were selected using a random sample from the sample frame of list of patients seen at those facilities.

Serum samples were processed and refrigerated within three hours of venipuncture. The serum samples that were not assayed within 24 hours after collection, were stored at 2°C to 8°C. Specimens held for longer were stored at -70°C. Serum total alkaline phosphatase, calcium, phosphorus, albumin, uric acid, urea and creatinine were measured by standard laboratory methods using the c8000 Architect (Abbott Diagnostic). Intact PTH was measured by chemiluminescence immunometric assays (Diagnostic Products Corporation, Ca USA) (14).

The laboratory analysis was done in the Department of Pathology at the UHWI. The equipments that were available for the test were the IM<sub>x</sub> (Abbott Diagnostics, USA) and c8000 Architect (Abbott Diagnostic; USA).

Data analysis was conducted using the statistical package for the social sciences (SPSS) version 17.0 (SPSS Inc, Chicago, Illinois, USA). The differences in distribution of demographic, clinical and pathologic variables between the two groups of patients were evaluated. Pearson's chi-squared test and Spearman's rho correlation coefficient test were used with  $p < 0.01$  which was considered statistically significant. Specificity, sensitivity and accuracy of diagnostic modalities were calculated. Pearson's correlation coefficient ( $r$ ) was determined for regression analysis.

Using the PubMed database, a systematic review of the literature for studies describing the distribution of ROD among CKD patients on dialysis and CKD patients not on dialysis was conducted as [search 1: kidney failure, chronic (MeSH) AND renal osteodystrophy (MeSH); search 2: renal osteodystrophy (MeSH) and biochemical markers; search 3: kidney failure, chronic (MeSH) AND biochemical markers and bone histomorphometry; search 4: dialysis (MeSH) and biochemical markers and bone histology].

Of all the retrieved results, articles published between 1985 and 2007 that provided information on bone histology in combination with serum biochemical markers of patients with CKD were selected. Of these 41 articles, 13 studies that had at least 3 of these 7 serum biochemical markers: PTH, Ca, P, ALP, bsALP, OC and vitamin D were selected. Because serum biochemical markers were expressed either as mean  $\pm$  standard deviation (SD) or standard error (SE), the SE was converted to SD by using the formula  $SE = SD/n$ . A weighted average of the mean and SD were calculated. To calculate the mean, the number of patients in each category was multiplied by the means of the serum biochemical markers and divided by the total number of patients in the study.

To calculate the weighted standard deviation, the second power of each standard deviation was added and then the square root of the sum was taken.

The patients were divided into those with high-turnover (HTO) bone disease and those with low-turnover (LTO) bone disease, according to the serum levels of intact PTH. The weighted average for serum biochemical markers in each category was calculated.

## RESULTS

The sample consisted of 458 patients. There were 221 patients (48.3%) in the CKD group and 237 (51.7%) in the control group. The majority of the patients in the CKD group were female (57.9%) and likewise in the control group (73.8%). The age group category of 60–69 years had the majority of patients in the CKD age category while the majority of the controls were in the 50–59-year age group. The mean age for the subjects in the control (51.0 years) and patients in the CKD (51.1 years) group were similar.

Most of the patients in the CKD group had normal weight (51.1%) followed by being overweight (27.6%) and obese (12.2%), the remainder were in the underweight category (9.1%). Similarly, the majority of subjects in the control group had normal weight (44.3%) followed by overweight (32.5%) and obesity (21.5%), only 1.7% of patients accounted for the underweight category. There were significant differences in the mean weight and BMI between the patients in the control and CKD groups. The mean (SD) weight of patients in the CKD group was  $68.9 \pm 14.9$  kg, which was significantly lower than that of the patients in the control group that had mean weight of  $74.7 \pm 13.8$  kg;  $p < 0.0001$ . Similarly, the mean (SD) BMI of patients in the CKD group was  $24.5 \pm 4.8$  kg/m<sup>2</sup> which was significantly lower than that of the patients in the control group that had mean BMI of  $26.6 \pm 5.3$  kg/m<sup>2</sup>;  $p < 0.05$  (Table 1). There were no significant differences in height between the patients in the control and CKD groups (Table 1).

Table 1: Demographic variables of control and CKD patients

Variables	CKD group		Control group		Significance
	Mean	SD	Mean	SD	
Age	51.1	16.4	51.0	19.3	$p > 0.05$
Weight	68.9	14.9	74.7	13.8	$p < 0.05$
Height	167.2	10.8	167.8	7.9	$p > 0.05$
BMI	24.5	4.8	26.6	5.3	$p < 0.05$

Statistical Significance was taken as  $p < 0.001$

As shown in Fig. 1, hypertension was the commonest cause of chronic renal failure (19.2%), followed by diabetes mellitus (10.0%), chronic glomerulonephritis (4.4%) and systemic lupus erythematosus [SLE] (3.3%). It was also

observed that autosomal dominant polycystic kidney disease (PKD) and obstructive uropathy accounted for 2.6% of all causes, respectively, whereas human immunodeficiency virus (HIV) was of a much less important cause (0.4%). The other causes of CKD in all the patients in the study are also represented in Fig. 1.

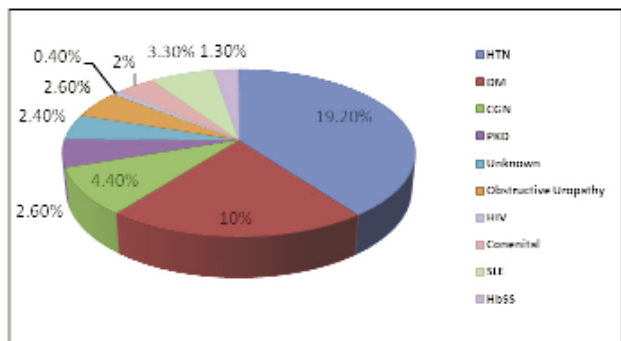


Fig. 1: Causes of chronic kidney disease

As shown in Figure 2, obstructive uropathy most commonly affected male patients (91.7%). The other causes

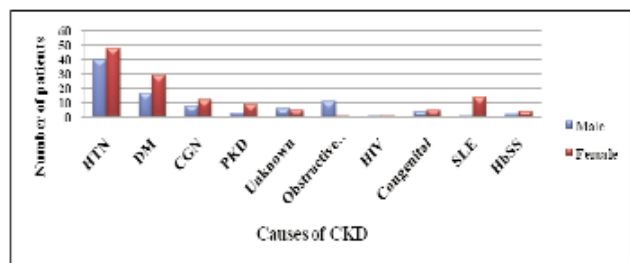


Fig. 2: Causes of chronic kidney disease by gender

of CKD were found mostly in female patients who represented as much as 57.47% of the entire population of patients with CKD.

The study population of patients in the CKD group receiving dialysis were at UHWI (32.6%), DARU haemodialysis unit (26.7%) and peritoneal dialysis at UHWI comprised 5.9% (Table 2).

Table 2: Dialysis site and type of treatment

Dialysis site/Unit	CKD group N (%)	Control Group N (%)
None	64 (29.0%)	237 (100.0%)
UHWI HDU	72 (32.6%)	0 (0.0%)
UHWI PDU	13 (5.9%)	0 (0.0%)
DARU HDU	59 (26.7%)	0 (0.0%)
St Joseph HDU	13 (5.9%)	0 (0.0%)

There were significant differences in the serum urea and creatinine concentrations between the patients in the control and CKD groups. The mean serum urea concentration of

patients in the CKD group was  $16.79 \pm 0.78$  mmol/L compared with  $4.93 \pm 0.20$  mmol/L in patients in the control group,  $p < 0.0001$ . Similarly, the mean serum creatinine concentration of patients in the CKD group was  $611.45 \pm 31.47$   $\mu$ mol/L compared with  $93.06 \pm 1.80$   $\mu$ mol/L in patients in the control group,  $p < 0.0001$ .

The serum tALP and iPTH in patients with CKD were significantly different from those in patients in the control group. The mean serum tALP levels of patients in the CKD group was  $144.51 \pm 12.38$  U/L compared with  $71.10 \pm 1.83$  U/L in patients in the control group,  $p < 0.0001$ . The mean serum iPTH levels of patients in the CKD group was  $52.75 \pm 4.47$  pmol/L compared with  $2.41 \pm 0.17$  pmol/L,  $p < 0.0001$ . There were significant differences in the serum phosphorus and albumin concentrations between the patients in the control and CKD groups. The mean serum phosphorous concentration of patients in the CKD group ( $1.48 \pm 0.05$  mmol/L) was significantly lower than that in patients in the control group ( $1.80 \pm 0.06$  mmol/L,  $p < 0.0001$ ). Similarly, the mean serum albumin concentration of patients in the CKD group ( $37.79 \pm 0.62$  g/L) was significantly lower than that in patients in the control group ( $46.89 \pm 0.27$  g/L,  $p < 0.0001$ ).

There were no significant differences in the serum uric acid and calcium concentrations between the patients in the control and CKD groups. Based on the results of serum IPTH, both the CKD and control groups were subdivided to determine the presence or absence of bone disease. A total of 174 patients in the CKD group were found to have bone disease (78.7%). The majority of patients in the control group did not have bone disease representing as much as 97.5% versus 2.5% of those patients who were found to have bone disease, meaning that, only 6 patients in the said group had diseased bones. Therefore, there were a total of 180 patients with bone disease in the study most of them were in the CKD group (Table 3).

Table 3: Bone disease based on serum iPTH for CKD and control groups

	Bone Disease based on iPTH		Total
	No Bone disease based on iPTH	Bone disease based on iPTH	
CKD Group	47 (21.3%)	174 (78.7%)	221 (100%)
Control Group	231 (97.5%)	6 (2.5%)	237 (100%)
Total	278	180	458

On further analysis of iPTH, of the 174 patients with bone disease in the CKD group, 51 (29.3%) had low bone turnover and 123 (70.7%) had high bone turnover disease (Table 4).

Further analysis of the remaining laboratory data was carried out to determine those parameters which could pre-

Table 4: Low and high bone turnover disease in CKD patients

Variable	Type of bone disease based on iPTH		Total
	Low bone turnover	High bone turnover	
CKD Group	51	123	174
	29.3%	70.7%	100.0%

dict bone disease in CKD. The serum tALP was found to be the only biochemical parameter that predicted the presence of bone disease. ( $p < 0.005$ , or 1.007, CI 1.002, 1012)

Pearson correlation demonstrated that there was a significant correlation between tALP and iPTH  $p < 0.001$  (2-tailed). Therefore, tALP can be used as a predictor of bone disease in patients with chronic renal failure when combined with iPTH. High turnover bone disease accounted for 68.9% in the CKD group when compared with low turnover bone disease (31.1%).

High turnover bone disease was more common in patients receiving haemodialysis, accounting for 75.9% when compared with 24.1% of those with low turnover bone disease. Fifty per cent of patients receiving peritoneal dialysis treatment were noted to have LTO and HTO bone disease respectively (Table 5).

Table 5: Type of bone disease *versus* renal replacement therapy modality.

RRT	Type of bone disease		Total
	LTO	HTO	
None	13	16	29
	44.8%	55.2%	100.0%
HD	32	101	133
	24.1%	75.9%	100.0%
PD	6	6	12
	50.0%	50.0%	100.0%
Total	51	123	174

Pearson chi-square.  $p = 0.003$

The tALP was analyzed in the CKD patients with bone disease. A total of 82.8% of patients receiving HD had the highest value of tALP. This was followed by 17 patients in the study that were not receiving RRT, accounting for 9.8%. There was a total 13 (7.4%) patients in the PD group with elevated tALP

## DISCUSSION

The main goal was to evaluate the prevalence of ROD and establish an association between serum biochemical markers associated with the rate of bone turnover such as iPTH with tALP, phosphorus, urea, uric acid, creatinine, calcium and albumin in order to establish an accurate diagnosis of ROD

which is essential to assign treatment. The data analysed showed that hyperparathyroid bone disease was the most common type of ROD in both CKD patients on dialysis and in those not on dialysis. The serum levels of iPTH and tALP were significantly higher in those patients with high turnover bone disease than in those with low turnover bone disease, regardless of RRT modality. Various methods such as serum biochemical markers, imaging studies and histopathological studies are currently used to diagnose ROD. The levels of iPTH, ALP, phosphorus, urea, uric acid, creatinine, calcium and albumin are among the most commonly used serum biochemical markers. Similar to previous studies, we found no significant association between serum calcium, phosphorus and uric acid with rate of bone turnover in ROD (15, 16).

Serum levels of PTH can predict the presence and severity of secondary hyperparathyroidism without correlating with the underlying bone disease (17–18). Levels of iPTH in dialysis patients more than 4 times normal and less than 2 times normal are associated with a greater frequency of HTO and LTO bone disease, respectively (19). Although PTH is a good indicator of bone metabolism, the sensitivity and specificity to diagnose high turnover bone disease with levels  $< 500$  ng/mL and ABD disease with levels  $< 100$  ng/mL are inadequate. Twenty-eight bone biopsy studies among dialysis patients revealed that bone remodelling and response to PTH varies among various racial groups (20, 21). In a study of 76 ESRD patients, the majority of African American patients with low turnover bone disease had higher serum PTH levels than those of Caucasians with low turnover bone disease (20). In this systematic review, although individual patients had variations in the correlation of PTH with underlying bone turnover, at an aggregate level there was a good correlation between the level of PTH and bone turnover between both dialysis and non-dialysis patients.

Alkaline phosphatase is a marker of osteoblast-mediated bone formation that provides useful information in conjunction with PTH measurement (22). The combination of low serum bsALP ( $\leq 7$  ng/mL) and low serum PTH is very suggestive of LTO bone disease (23). Similarly, an elevated bsALP ( $> 200$  ng/mL) alone or in combination with increased serum PTH ( $> 200$  ng/mL) has been shown to be highly sensitive and specific for HTO bone disease (24). Although bsALP may provide some advantage, some experts believe that total serum ALP plus PTH levels are adequate to evaluate bone formation (25). In this review, there was a good correlation between serum ALP and bone turnover among dialysis patients; however, such correlation was not present among CKD patients not on dialysis. Total ALP, an indicator of osteoblastic activity, was not reported in all articles used in this review. However, based on the data, there was a good correlation between tALP and bone turnover. In dialysis patients with high turnover bone disease, the levels of tALP were almost four times higher than those in low turnover bone disease in the present study. Similarly, in CKD patients not on dialysis with high turnover bone disease, the levels of

tALP were almost double that of those with low turnover bone disease. The serum level of osteocalcin (OC) – an indicator of bone formation reflects the rate of OC synthesis by osteoblasts. Among biomarkers, which reflect bone formation, the OC assay is preferred because of its high discriminant power and is better characterized in terms of clinical application (26). Osteocalcin was reported in a limited number of articles, however, using the aggregate data, there should be a good correlation between level of OC and bone turnover. It should be expected that among dialysis patients with high turnover bone disease, OC levels might be almost three times greater than those in low turnover bone disease. Similarly, in CKD patients not on dialysis with high turnover bone disease, the levels of OC might be almost twice those of patients with low turnover bone disease (26). The study has shown, that on a collective basis, serum levels of iPTH and tALP, and possibly osteocalcin are high in high turnover bone disease and low in low turnover bone disease. Use of a combination of 2 or more markers may determine underlying renal osteodystrophy with more accuracy than individual biochemical markers. However, a bone biopsy should be encouraged in younger patients with ESRD, with PTH levels between 200 and 500 pg/dL where other biochemical markers are not well defined.

The limitations of this study were small sample size. The CKD group and the control group were not matched for age, gender and BMI. The osteocalcin and bone specific alkaline phosphatase reagents were not available for this study.

In summary, the most common type of ROD based on serum biochemical markers among dialysis and CKD patients not on dialysis was high turnover bone disease; however, the presence of low turnover bone disease was significant in both groups. A combination of two or three serum biochemical markers such as PTH, ALP, bsALP, and OC might help clinicians to diagnose ROD more accurately in order to assign treatment with vitamin D.

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