Okeke *et al*

Chronic Renal Failure and Tending Skeletal Pathology in Patients on Dialysis Treatment

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ABSTRACT

Background: Chronic renal failure (CRF) is becoming one of the leading causes of morbidity and mortality in sub-Saharan region. This study was carried out to investigate the status of the bone tissue in the chronic renal failure (CRF) patients in Eastern part of Nigeria.

Method: 124 subjects were used in this study. Half of them were chronic renal failure patients on dialysis treatment while the other half was apparently healthy subjects. Blood samples were collected and their serum urea, creatinine, alkaline phosphatase, calcium, phosphate were assayed using spectrophotometric method. **Results**: The urea and creatinine values of the CRF patients (16.8 ± 1.2mmol/l and 363.4 ± 26 umol/l respectively) were significantly higher than (P ≤ 0.05) those of the healthy subjects (urea: 3.8 ± 0.1mmol/l and creatinine: 66.1 ± 2.3umol/l). Calcium value of CRF patients (1.4 ± 0.1mmol/l) was significantly lower than (P ≤ 0.05) that of the healthy individuals (2.7 ± 0.2mmol/l). There was insignificantly lower value (P ≥ 0.05) of the phosphate in the healthy subjects (2.26 ± 0.2 mmol/l) than that of chronic renal failure patients (3.1 ± 0.5 mmol/l). Serum enzyme, alkaline phosphatase was observed to be significantly higher (P ≤ 0.05) in CRF patients (52.4 ± 1.9 iu/l) than in healthy individuals (41.4 ± 2.8 iu/l).

Conclusion: The hypocalcaemia, higher phosphate levels, and accompanied elevated alkaline phosphatase show that there should be compensatory mechanism of bone resorption to handle the presenting hypocalcaemia. The dynamism in these bone biomarkers indicates that the chronic renal failure definitly predispose the patients, though on dialysis treatment, to skeletal fragility.

Key words: chronic renal failure, bone, calcium, phosphate and alkaline phosphatase

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Author's contributions: This work was carried out and approved in collaboration between all the authors, who take responsibility for its accuracy and integrity. CUO, PUA designed the study; CCE, ANO sourced for funding; CUO wrote the protocol; CUO, CCE, contributed in literature search; PUA, CCE, ANO did Lab experiments; PUA, CCE ANO did the statistical data analysis; PUA, ANO contributed in discussions; CUO drafted the manuscript; CUO supervised the study; CUO wrote the final manuscript; CUO proof read the final version for publication.

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Okeke *et al*

INTRODUCTION

Metabolic bone disease is one of common complications of chronic renal failure. It is also part of a broad spectrum of disorders of mineral metabolism that occur in renal disease. Renal failure most often results in both skeletal and extraskeletal consequences especially during chronic stage when management is poor. Chronic kidney disease is regarded as one of the major causes of increased rate of death (1) Control mechanisms for calcium and phosphorus homeostasis are usually altered in early course of chronic kidney disease and this adventedly progresses to poor skeletal metabolism.

Bone abnormalities in chronic renal failure include the effects of high levels of parathyroid hormone on bone, which results in osteitis fibrosa. It has been established that hyperplasia of the parathyroid glands, consequently high levels of parathormone in the blood occur early in the course of chronic renal failure (2,3). There is retention of phosphorus, reduction in 1,25-dihydroxycholecalciferol level, and hypocalcaemia in chronic renal disease. Phosphate has been presumed to affect parathyroid reaction independently of calcium or calcitriol. This possibility was demonstrated by Slatopolsky et al (4) and Almaden et al (5), and they independently stated that changes in extracellular phosphorus concentrations in vitro gave rise to an increased production of parathormone in the absence of changes in ionized calcium. Calcitriol is primarily produced in the kidney and consequent decrease in kidney mass leads to a decrease in the ability to produce calcitriol. Calcitriol levels seem to decline slowly and progressively throughout the course of CKD (6). In CKD, the decreased production of calcitriol results in the development of secondary hyperparathyroidism. But it has been observed that increase parathyroid hormone does not consequently cause high activity of 1-α- hydroxylase enzyme in the kidney (7). The decline in the activity of the enzyme has been attributed to phosphate retention, fibroblast growth factor 23, increased loss of vitamin D binding protein and some of these factors contribute to reduced calcitriol level (8,9). In some setting of CKD, especially in advanced stage, calcitriol decreases because of decrease in the vitamin D receptors in target tissue (10,11). Alkaline phosphatase (ALP) is a membrane bound zinc metalloprotein enzyme that split off a terminal phosphatase group from organic phosphate esters. Fifty percent of circulating ALP are organic of bone origin in a normal individual. Bone specific ALP iso enzyme can be of great diagnostic importance and its increase indicates increased osteoblastic activity seen in paget disease or rickets or osteomalacia (12).

Low- turnover bone disease commonly seen in renal disease patients, especially those on dialysis, is marked by extremely slow rate of osteogenesis. In some cases, there is defective bone mineralization coupled with very slow rate of bone formation. Some cases of osteomalacic lession in this group of patients are due mostly to aluminum accumulation.

In normal functioning kidneys, greater percentage of plasma phosphate (about 90%) is filtered and excreted in the urine (13). However, in patients with CKD, disorders that lead to Chronic Kidney Disease-Mineral Bone Disease (including secondary hyper-parathyroidism, hyperphosphatemia, decreased intestinal calcium absorption and disordered vitamin D metabolism) commences in stage 2, it is not detectable clinically until late stage 3 or early stage 4 (14, 15, 16). These bone cells, osteocytes and osteoblast have been identified to produce high levels of fibroblast growth factor 23 in chronic renal

failure patients (17). This and other mechanisms ensure normal calcium and phosphate homeostais in onset of chronic renal failure amid the parathyroid hormone increase. The patient's calcium and pH values remain normal until glomerular filtration rate goes below 50 ml/min/1.73 m^3 in stage 3 (15,18, 19). It has been stated that half of kidney function declines at stage 3, and this stimulates the nephrons to excrete phosphorus and the bones to release calcium. This would give rise to bone resorption, remodeling, and redistribution and osteitis fibrosis.

 In late stage 4 CKD, low blood levels of calcium and phosphate develops in response to decreased intestinal calcium absorption (from critically low calcitriol concentrations) and decreased phosphate excretion (from critically low renal mass), respectively (20). Metabolic acidosis is also one of the cascades of abnormalities that occur at stage four of chronic renal failure. This metabolic acidosis weakens bone further (16). To compensate this metabolic acidosis, calcium is secreted from bone to buffer excess hydrogen ions and this worsens the bone mineral density.

The abnormality of bone mineral density observed in chronic renal failure patients on dialysis treatment has drawn apt attention among many medical scientists especially in western societies. This study was carried out to investigate the bone status of chronic renal failure patients on dialysis treatment in Nigeria.

MATERIALS AND METHODS:

Hundred and twenty-four subjects voluntarily participated in this study. Sixty-two of them were known chronic renal failure patients on dialysis treatment from both Government and Private hospitals in Imo and Abia State Nigeria, while the rest 62 subjects were apparently healthy subjects randomly selected as control group. After obtaining the hospital management's and participants' consents, the subjects' blood samples were collected and serum levels of creatinine, urea, phosphate, calcium and alkaline phosphatase were estimated using spectrophotometric method.

The data collected were subjected to statistical analysis using Megastat 10.1 statistical software. The definitive statistics, Analysis of variance, student's t-test, probability testing (p-value), were obtained using Megastat.

RESULTS

In table 1, figure 1.1, and figure 1.2, the renal failure patients' serum creatinine (363.4 ± 26 umol/l) and urea (16.8 ± 1.2 mmol/l) were significantly higher (p ≤ 0.05) than the healthy patients' creatinine (66.1 ± 2.3 umol/l) and urea (3.8 ± 0.1 mmol/l) levels.

In the table 1 and figure 1.3, serum calcium level was significantly higher (p ≤ 0.05) in healthy subjects (2.7 ± 0.2mmol/l) than in renal failure patients (1.4 ± 0.1mmol/l).

As demonstrated in table 1 and figure 1.3, phosphate level had insignificant (p ≥ 0.05) change between the subject groups: 2.26 ± 0.2 mmol/l in healthy subjects and 3.1 ± 0.5 mmol/l in renal failure patient groups.

Alkaline phosphatase activity in renal failure patients (52.4 ± 1.9 u/l) was higher than that of the healthy subjects (41.4 ± 2.8 u/l) as shown in table 1 and figure 1.4

Table 1: The comparative results of the mean ± standard error of serum urea, creatinine, calcium, alkaline phosphatase, and phosphate of healthy subjects and chronic renal failure patients.

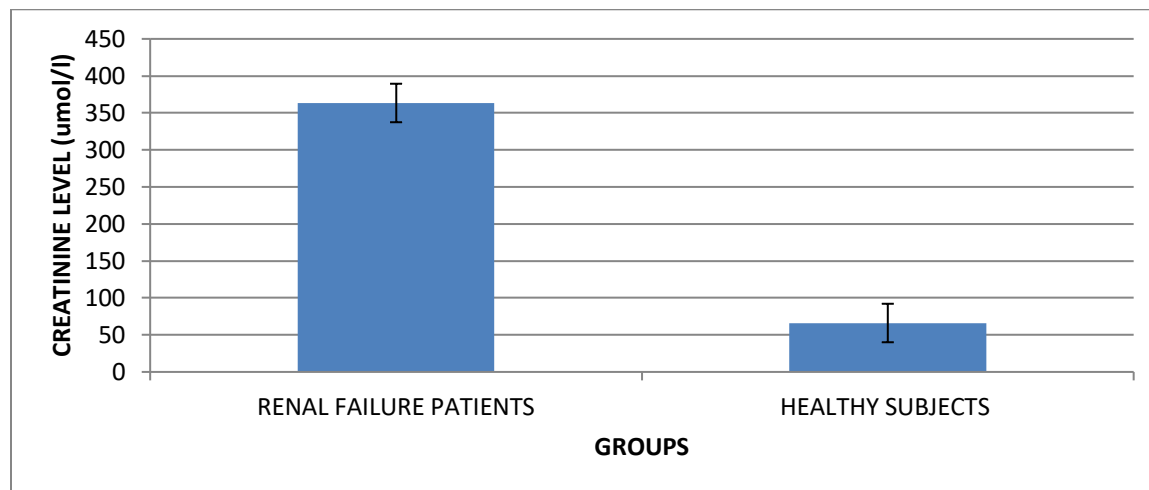| PARAMETERS	RENAL FAILURE PATIENTS (n=62)	HEALTHY SUBJECTS (n=62)	P-VALUE
UREA (mmol/l)	16.8 ± 1.2	3.8 ± 0.1	$P \leq 0.05$
CREATININE (umol/l)	363.4 ± 26	66.1 ± 2.3	$P \leq 0.05$
CALCIUM (mmol/l)	1.4 ± 0.1	2.7 ± 0.2	$P \leq 0.05$
PHOSPHATE (mmol/l)	3.1 ± 0.5	2.26 ± 0.2	$P \geq 0.05$
ALKALINE PHOSPHATASE (u/l)	52.4 ± 1.9	41.4 ± 2.8	$P \leq 0.05$

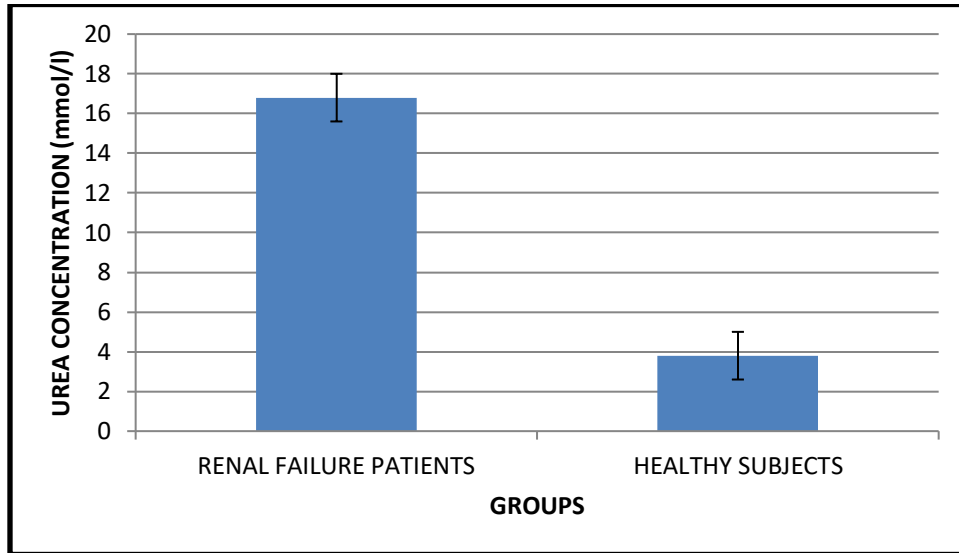**Figure1.1**: BAR CHART OF THE UREA LEVELS IN BOTH GROUPS OF SUBJECTS

Figure1.2: BAR CHART OF THE UREA LEVELS IN BOTH GROUPS OF SUBJECTS
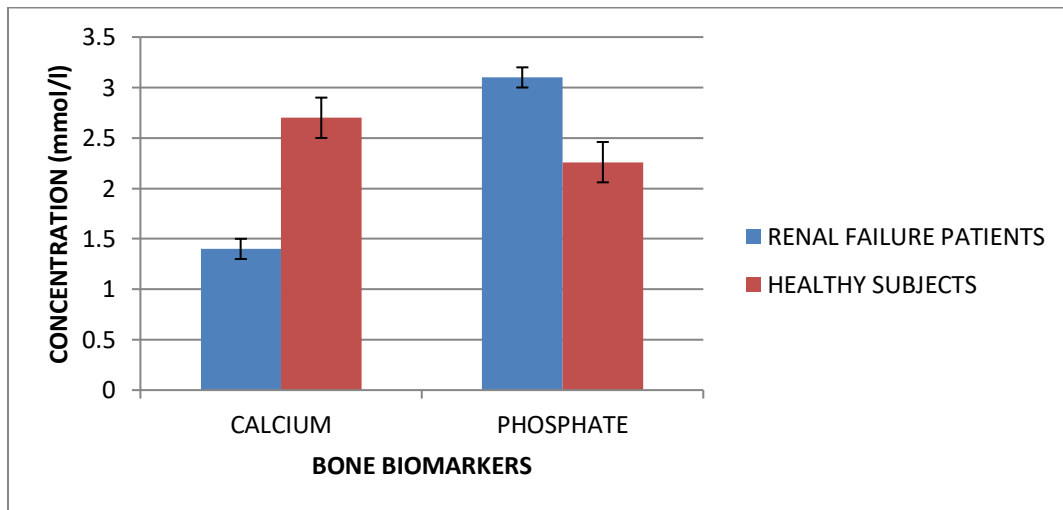

Figure1.3: HISTOGRAM OF THE LEVELS OF BONE BIOMARKERS (CALCIUM AND PHOSPHATE) IN BOTH GROUPS OF SUBJECTS
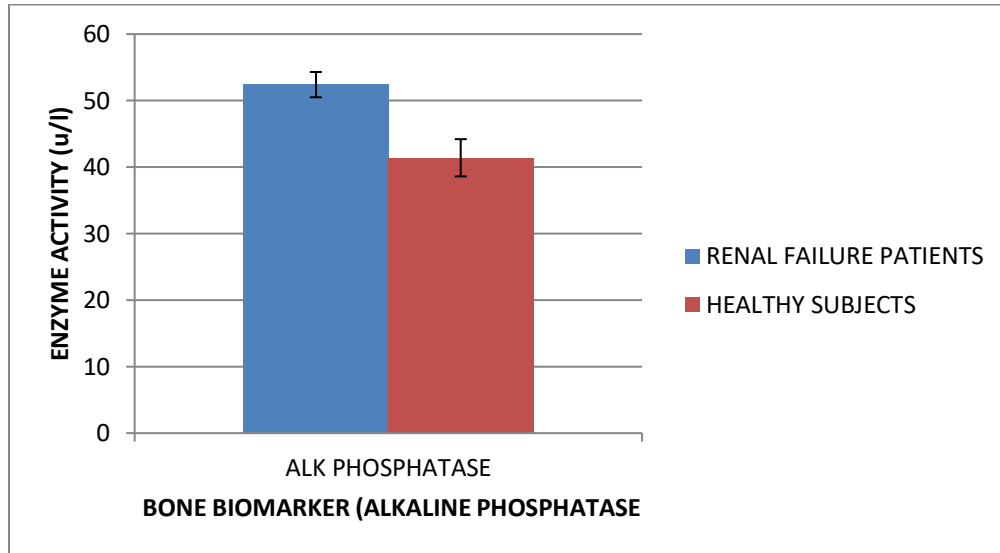
Figure1.4: HISTOGRAM OF THE LEVELS OF BONE BIOMARKERS (ALKALINE PHOSPHATASE) IN BOTH GROUPS OF SUBJECTS

DISCUSSION

Renal failure being a very debilitating illness has been classified to have a negative impact on bone health. The effect has been described as renal osteodystrophy as a result of diminished or hampered calcitriol production by the kidney tissues.

In this study among chronic renal failure patients in some hospitals in eastern part of Nigeria, it was observed that there were higher levels of alkaline phosphates and organic phosphate but a significant lower level of serum calcium compared to the healthy individuals. This was in agreement with finding in studies carried out among Caucasian chronic renal failure patients on dialysis (21). The increased alkaline phosphates level might be due to increased dephosphorylation of the skeletal tissues observed in bone resorption (22). The high serum level of akaline phosphatase associated with luxation of hip bone on hemodialysis of Japanese patients (23) was attributed to have been of bone origin. In the work carried out by Graciolls et al (21), it was observed that deterioration of kidney

resulted in progressive increase in bone resorption with decline in bone formation and mineralization.

In the event of increased dephosphylation of osseous tissues in chronic renal facture the serum phosphate is increased which consequently results in descreased renal excertion of inorganic phosphate (24). Kidney normally plays essential role in phosphate excretion from the vascular pool, and any injury to the kidney, affects clearance of phosphate from the vascular system and this adventedly increases the serum phosphate level seen kidney disease (24). In this study, though the phosphate level was higher in renal disease patients than in normal subjects, the raised level was not significant. This non-significant increase might be as a result of influence of fibroblast growth factor 23 (25) on phosphate excretion. Fibroblast growth factor 23 (FGF23) is a counter-regulatory phosphaturic hormone for vitamin D. In chronic kidney disease, as glomerula filtration rate decreases, FGF23 production is increased. The increased secretion of this

protein, FGF23, enhances the excretion of phosphate seen in renal disease (26).

The increased phosphate level in CKD patient might also be as a result of effects of phosphate itself on proximal tublar sodium-dependent phosphate transport protein (Napiza) which increases the excretion of phosphate through the kidney (27)

Calcium, whose main storage reservoir is bone, is demineralized into the blood stream during bone resorption by the osteoclastic cells and as a result causes hyper-calcaemia in chronic renal disease. This increased resorption in renal failure cases gives rise to bone disorder referred to as renal osteodystrophy. This calcium metabolism obversed in renal failure contradicts the finding in this study. In this study, it was observed that serum calcium level of renal failure patients was significantly lower than that of healthy subjects. The study conducted in Ile-ife Nigeria by Sanusi et al (28) corresponds with hypocalceamia observed in this study. The low calcium level observed in the renal disease patients might be attributed to reduced calcium absorption as a result of reduced calcitriol production in kidney failure (29). In some cases, hypocalcaemia seen in renal disease may be caused by excessive transfusion of citrated blood products which temporally reduces the ionized calcium until the citrate in the transfused blood is cleared by the liver (29). The low calcium level seen might be caused by intake of some diereties used in chornic kidney disease. Madhu & Dolores (29) also stated that magnesium deficiency could also cause hypocalcemia in renal failure as magnesium interfers with the end-organ actions of parathyroid hormone and / or by inhibiting its secretion. The exact cause of this low calcium level observed in chronic renal failure paitient on dialysis was not determined in this study. Calcium balance during dialysis session is very important because negative balance of extracellular calcium will result in hypocalcemia. The decree of the hypocalcemia should be noted as this may affect the patient's heart and skeletal system.

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