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Secondary Hyperparathyroidism and Hypocalcaemia in Dialysis Patients in Kano

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ABSTRACT

The Aminu Kano Teaching Hospital (AKTH) is one of the tertiary health institutions in Nigeria where dialysis is provided to patients with chronic renal disease, but there had been no reported study on the prevalence of biochemical indicators of bone and mineral metabolism in these patients. We measured serum parathyroid hormone (PTH), total calcium (Ca), albumin (ALB) and phosphate (P) and calculated calcium – phosphate (CaP) ion product in order to evaluate parathyroid function and bone mineral status in dialysis patients seen at the AKTH, Kano. Forty five patients and fourty-five healthy age matched hospital staff who served as controls were studied. Intact PTH was measured with a commercial kit which is based on immunoassay (DRG International Incorp, USA) while serum calcium, phosphate and albumin were estimated also with commercial kits (Randox Laboratories, UK). Calcium was corrected for albumin.The mean PTH of 194 pg/mL in dialysis patients was significantly higher ($P< 0.001$) than 28 pg/mL found in controls. The corrected calcium was 1.81 mmol/L, phosphate 2.26 mmol/L, albumin 27.09 g/L and CaP product 3.35 $mmol^2/L^2$ in dialysis patients compared to calcium of 2.46 mmol/L, phosphate 1.04 mmol/L, albumin 42.78 g/L and CaP product of 2.55 $mmol^2/L^2$ in controls. Fourty eight percent of the patients had secondary hyperparathyroidism, 89% hypocalcaemia, 53% hyperphosphataemia, 82% hypoalbuminaemia and 29% elevated CaP product. This study has demonstrated significant abnormality of calcium, phosphate and parathyroid homeostasis in patients undergoing dialysis in Kano. As persistent elevations of PTH, phosphate, CaP product and co-existing hypocalcaemia are known to contribute to morbidity and mortality in dialysis patients, it is recommended that pharmacological correction and routine measurement of these biochemical indicators be instituted for management of haemodialysis patients in our hospitals.

KEYWORDS: *Hyperparathyroidism, hyperphosphataemia, calcitriol, extraskeletal calcifications, dialysis.*

INTRODUCTION

The existence of severe bone disease associated with chronic renal failure has been recognized for several decades. In the uraemic state, the process that maintains mineral and bone homeostasis is grossly impaired. The main features of this impairment include perturbations in mineral metabolism, bone morphology and bone composition [1]. This disabling complication develops as a result of secondary hyperparathyroidism and disruption of calcium-phosphate-bone interrelationships[2]. Parathyroid hormone (PTH) release that is attuned to normal calcium requirement becomes dominated by alterations in phosphate balance. With each wave of nephron destruction there occurs transient hypocalcaemia and a stepwise rise in PTH as well as decreased synthesis of 1,25 dihydroxycholecalciferol ($1,25(OH)_2D_3$), the active form of vitamin D_3, also known as calcitriol. Thus in patients on long term haemodialysis, if hyperphosphataemia and hypocalcaemia persists, PTH may remain high and osteitis fibrosa cystica (OFC) and osteomalacia may progress. Hyperphosphataemia, elevated calcium - phosphate (CaP) ion product and increased PTH have been associated with increased mortality in patients with end stage renal disease [3, 4] as a result of the calcification that occurs in visceral, vascular and other soft tissues. Of prominence is the coronary artery

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calcification, a condition usually associated with increased cardiac mortality that is quite severe and highly prevalent, especially among young dialysis patients [5].

Maintenance haemodialysis for patients with chronic renal failure has been instituted in Aminu Kano Teaching Hospital (AKTH), Kano for almost a decade. This study was undertaken to examine parathyroid hormone and calcium - phosphate profile in the dialysis patients seen at the hospital. It is hoped that this would contribute to our understanding of mineral and bone homeostasis as well as providing biochemical markers for better management of these patients.

MATERIALS AND METHODS

This study involved fourty five patients who were undergoing haemodialysis at AKTH, Kano.The patients were consecutively recruited based on the usual criteria for dialysis in the Hospital which include elevated serum creatinine and urea with creatinine clearance falling below 30mL/min in addition to other features of end - stage renal disease (ESRD). Patients with acute renal failure were excluded from the study.

Maintenance haemodialysis in this hospital is usually carried out with a Fresenius polysulfone UF 5.5 (Fresenius medical care, Humburg), by the attending nephrologists and nurses with each session lasting for four hours. Dialysis sessions were irregular for most of the patients studied due to financial constraints and only a few could afford the three times dialysis sessions per week and the prescribed phosphate binders, calcium supplements or oral á-calcidiol due to the same reason. Fourty five healthy age matched hospital staff served as controls. Informed consent of each subject was obtained for the study which was approved by the Ethical Committee of the Hospital.

In each subject, blood was collected into lavender EDTA tube and plasma was promptly seperated and stored frozen at –20° C until analysed for PTH. For calcium, phosphate and albumin estimations, blood was collected without venous stasis into plain tubes and serum harvested and stored frozen at –20°C until analysis. Serum intact PTH was estimated in one batch with a commercial kit supplied by DRG International Incorp, USA which is based on enzyme immunoassay employing enzyme linked immunosorbent technique (ELISA). Measurement of serum total calcium, phosphate and albumin were performed using commercial kits obtained from Randox Laboratories, UK. Creatinine clearance results were below 10mL/min in all the patients.

The results of PTH were log transformed and the sum of mean plus or minus two standard deviation (log mean ± 2 log SD) was used to establish 95% confidence interval for the analyte. Two levels (medium and high) of lyophilized synthetic human-PTH (h-PTH, 1-84) control sera were analysed each in duplicate during the assay for PTH to assess quality of the results. The average values (medium 67 pg/mL, high 270 pg/mL) were within acceptable ranges (medium 54.7 - 68.5 pg/mL, high 251 – 312 pg/mL) quoted by the manufacturer. For calcium, phosphate and albumin, one level (medium) commercial control sera from Bio-Rad Diagnostic Group, (Irvine USA), was used for quality assurance and precision studies and coefficients of variation obtained were within acceptable limits. Results for albumin was used to obtain corrected total calcium values as described by Walmsley and White (1985) [6]. Statistical mean, standard deviation (SD) and standard error of mean (SEM) were calculated and comparison between patient and control values were assessed by Student t test.

Hyperparathyroidism was defined as serum intact PTH greater than 210 pg/mL, hypocalcaemia as serum total calcium less than 2.12 mmol/L, hypoalbuminaemia as albumin less than 30 g/L, hyperphosphataemia as serum phosphate greater than 2.10 mmol/L and increased CaP product as CaP greater than 4.44 $mmol^2/L^2$.

RESULTS

Biodata and reported causes of chronic renal failure in the study population are shown in Table 1. The mean age of the patients was 44 years while that of the controls was 45. The table shows the predominance of males (76%) over females (24%) and hypertension to be the major cause of chronic renal disease accounting for 47%.

The geometric mean, 95% confidence interval for intact PTH, as well as the mean, standard deviation and 95% confidence interval for serum total calcium, phosphate, and albumin and CaP product for patients and controls are shown in Table 2. Mean concentrations of intact PTH, phosphate and CaP product were significantly higher ($P < 0.001$) and calcium and albumin significantly lower ($P < 0.001$) **Table**

1: Characteristics of the study population

	Patients	Controls
n	45	45
Males	34(76)	34(76)
Females	11(24)	11(24)
Hausa-Fulani	29(64)	43(96)
Yoruba	5(11)	0(-)
Igbo	3(7)	1(2)
Others	8(18)	1(2)
Causes of chronic renal failure		
Hypertension	21(47)	
Diabetes mellitus	8(18)	
Glomerulonephritis	3(7)	
Polycystic kidney disease	1(2)	
Others	12(26)	

Number in brackets indicate percentage

in the dialysis patients compared to controls (Table 2). The proportion of patients with abnormal serum PTH, total calcium, phosphate, and albumin and CaP product is shown in Table 3. In contrast, no abnormalites were found in any of these indices in control subjects.

DISCUSSION

In chronic renal failure, mechanisms responsible for the maintenance of normal mineral and bone metabolism are impaired. The kidneys are unable to excrete phosphate, produce adequate calcitriol and maintain calcium balance. These biochemical abnormalities promote the development of secondary hyperparathyroidism and its complications. Inadequate control of serum phosphate and calcium in these patients is essential in the development of a variety of disturbing clinical conditions which include cardiovascular and soft tissue calcifications, calciphylaxis and renal osteodystrophy as a result of elevated CaP ion product and PTH. An important clinical problem in these patients is hyperphosphataemia which contributes to high morbidity and mortality [3, 4, 5].

Persistently elevated levels of PTH characterize secondary hyperparathyroidism. What is considered elevated PTH needs to be defined.

Table 2: Biochemical parameters of patients and controls subjects

	Patients	Controls	
Parameter	Mean ±SD (95% CI)	Mean ±SD (95% CI)	p value
Calcium	1.81± 0.39 (1.03 – 2.59)	2.46± 0.16 (2.14 – 2.78)	<0.0001
Phosphate	2.26± 1.02 (0.22 – 4.30)	1.04± 0.25 (0.54 – 1.54)	<0.0001
PTH	194.13± 0.41 (29 – 1300)	27.52±0.203 (10.78 – 70.21)	<0.0001
CaP	3.35± 1.36 (0.63 – 6.07)	2.55± 0.66 (2.31 – 2.69)	<0.0001
Albumin	27.09± 5.94 (15.21 – 38.97)	42.78± 7.24 (28.30 – 57.26)	<0.0001

Table 3: Proportion of dialysis patients with abnormal serum parathyroid hormone, calcium, albumin, phosphate and CaP ion product in Kano

Patients with	(n)	(%)
Hyperparathyroidism	20	48
Hypocalcaemia	40	89
Hypoalbuminaemia	37	82
Hyperphosphataemia	24	53
Increased CaP ion product	13	29

Several reports [4, 7] suggesst that optimal levels of intact PTH necessary for normal bone histology and function range between two to three times the upper reference limit of normal subjects. Based on 70pg/mL, an intact PTH level greater than 210 pg/mL would be considered elevated in our patients, 48% of who had secondary hyperparathyroidism (Table III). There is a close similarity between this finding and the report from a US dialysis population [8], in which 50% had secondary hyperparathyroidism. The similarity in prevalence has been attributed to the fact that more than 90% of the US patients were African Americans with similar episodes of dialysis skipping, though due to different reasons. In constrast, prevalence of secondary hyperparathyroidism in dialysis patients seem to be lower in the Caucasins as seen by reports from Italy and Spain [9, 10]. Ethinic differences appear to be important in parathyroid function relative to vitamin D status and bone tissue response to PTH[11] and this need to be given due consideration in the evaluation of African dialysis patients. Complications of persistently elevated levels of PTH, which has been demostrated in experimental animals, include increased levels of cytosolic calcium [12], thickening of arteriolar wall and myocardial fibrosis, increased triglyceride and LDL cholesterol, decreased HDL cholesterol and worsening hypertension [5, 13]. These abnomalities are believed to be the basis of organ dysfunction and cardiovascular morbidity and mortality in this disorder.

It has been observed that serum phosphate greater than 2.10 mmol/L in haemodialysis patients is associated with increased risk of death [3]. The present study indicates that 53% of our patients had serum phosphate greater than this value (Table 3) compared to a figure of 50% hyperphosphataemia in such patients seen in Italy [8]. In many instances, dialysis procedures are not efficient enough to remove all the dietary phosphate absorbed from the intestine hence contributing to hyperphosphataemia [14]. As excessive reduction of dietary phosphate may jeopardize adequate protein nutrition, it has been demostrated that pharmacological intervention with phosphate binders, in addition to dialysis, is beneficial in the control of hyperphosphataemia and in the treatment of secondary hyperparathyroidism in uraemic patients [15]. Hypocalcaemia defined in dialysis patients as serum calcium lower than 2.12 mmol/L[4], was found in almost 90% of the patients in this study (Table 3), a figure much higher than reports from the USA [8] (17%), Italy [9] (27%) and Spain [10] (23%).The high prevalence of hypocalcaemia in our patients could be due to inadequate dialysis sessions, inability to absorb dietary calcium due to lack of calcitriol production by the failing kidneys and the fact that only few patients could afford á - calcidiol or other vitamin D analogues prescribed in the management of these patients. Elevated levels of CaP product has been shown to positively influence cardiac, vascular, periarticular, soft tissue and parenchymal calcifications [3, 4, 16] and increased risk of death if there is coexisting hyperphosphataemia. Almost 30% of our patients had elevated CaP product (Table 3) and most of who had hyperphosphataemia. Studies by Partiff [17] have shown that the magnitude of CaP product correlates with the incidence of calcifications. Anderson[18] further described a final common pathway for calcific diseases. In most instances, the initial calcification occurs in the mitochondria, which serves as the nucleus for crystal proliferation both intracellularly and extracellularly. Calcifications of large arteries, valves and atherosclerotic plaques may also occur. In these situations, membrane vesicles that are exocytosed from aging or damaged smooth muscle cells within the lipid-rich atherosclerotic plaque can serve as the initial site of apatite deposition[19]. This phenomenon could account for the high CaP product observed in this study and could be responsible for poor prognosis.

The findings in this study are a reflection of the inadequate dialysis and inability to procure necessary drugs such as á-calcidiol and calcium supplements by most of the patients and this suggest a strong need for routine correction and measurement of these biochemical indices of bone metabolism in our dialysis patients.

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