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TITLE: "RENAL OSTEODYSTROPHY AS SEFN AT KENYATTA NATIONAL HOSPITAL.

BY

NAME: dr. J.H.'swag M.B.,Ch.B (NAIROBI 1978)

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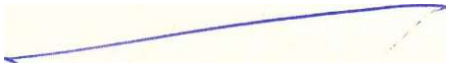
A DISSERTATION SUBMITTED IN PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE (MEDICINE) IN THE UNIVERSITY OF NAIROBI.

©lis dissertation is my original work and has not been presented for a degree in any other University.



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This dissertation has been submitted for examination with my approval as University supervisor.

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I

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CONTENTS

SlIKMARY

31 patients (17 males and 14 females) were studied* Clinical renal osteodystrophy, taken as bone tenderness with restricted joint movements, was found in 21(67.7%) patients and there was no difference between the two sexes. Clinical renal osteodystrophy was found among all the ago groups studied (15 to 50 years)® Pain in the lumbar and long bones were a-RTong the most frequent and consistent early complaint^. Serial skeletal x-rays_r_taken-, were all reported normal. The mean duration of illness of patients with clinical renal osteodystrophy was 36.5 ± 13»9 months and this was found to be significant (.Ol^P< .025)• Biochemical renal osteodystrophy, taken as raised sei'um alkaline phosphatase (mean 182.4 + 39*1 mmol/l) and serum inorganic phosphate (mean 3*36 ± 1.25tnmol/l) , was found in l8 (58.1?o) of 31 patients. There was significant correlation between creatinine clearance (mean 10.29± 15.lml/min) and biochemical renal osteodystrophy (P .01) .

INTRODUCTION AND itKVIKW OF LITERATURE

» definition

The terminology; renal osteodystrophy, was first proposed for bone changes (rickets, osteomalacia, osteitis fibrosa cystica) in chronic renal failure by Liu and Chu (19^3) (l). Later tfanley D.A. **(1978) (2)** gave a more comprehensive definition as a term given to bone disease (3) in renal failure characterized by a combination of four possible forma: osteitis fibrosa cystica (classical hyperparathyroid bone disease), osteomalacia (excessive quantity of uncalcified bone matrix or osteid) osteopenia (decreased bone mass), and osteosclerosis (increased bone density (2)b

2• Historical baclcgro1md of rena1 ostepd.ystrophy»

The association between kidney disease and bone deformity was first described by Clement Lucas in **1883***(h)*. He noted repeated detection of albuminuria in cases of curved spine and bent bones and concluded that the 3.ate rickets and albuminuria pre too frequently associated to be matters of chance and that albuminuria -is often tin important sign indicating the cause of bone deformity, Fletcher in **1911.(5),** Parson in **192? (6)**

both clinicians working in Britain showed keen interest in kidney disease and disorders of skeleton and defined the principal clinical and radiological features of renal osteodystrophy both in children and adults. This condition was known as "renal dwarfism" "renal infantilism" and "renal l-icketa" or these terms were used to describe it (7)0 ^t was however obvious at that time that dietary deficiency of vitamin Li played no role in the pathogenesis of rachitic changes and that therapy with cod-liver oil had no curative value (6),

Albright et al described the first adult patients (8) with chronic azotaemic renal failure and skeleton changes similar to those of osteitis fibrosa of primary hyperparathyroidism. During the same year 1937? Park and Eliot also working in United States of America simultaneously demonstrated the lesions of osteitis fibrosa in children with renal rickets ($))» At this stage it was thought that renal osteitis fibrosa or renal hyperparathyroidism was the only bone changes occuring in renal osteodystrophy but this was later disapproved by Stanbury working in Britain in 1957 (7) when he reported on adult patients with chronic azotaemic renal failure who had florid osteomalacia, a counterpart of renal rickets. Prior to introduction

of haemodialysis, clinical bono disease was very rare as most patients used to die in the early stages of chronic renal failure (lO) a situation pertaining in Kenya now. Both maintenance haemodialysis and peritoneal dialysis were successfully performed in 19ᶻi0's (ll, 12) though with restricted application. Either of the two technique became widely used in i960's with subsequent prolongation of lives of patients who otherwise used to die before manifestation of renal osteodystrophy« Dialysis and renal transplantation have revolutionised the management of chronic renal failure and many patients with end - stage kidney disease are surviving for long times with some complications associated with prolongation of life in renal failure i.e. bone disease. Significant progress has been made in the pact few years concerning the understanding of pathophysiology of renal osteody-strophy.

3 * Pathophysiology and pathogenesis of renal osteody-strophy:

The mechanism responsible for the development of renal osteodystrophy in patients with chronic renal disease are multifactorial and poorly understood (l,2).

The manifestation of deranged mineral metabolism in uraemia include hypocal caetnia$_t$ hyjierphosphataemra , hyperplasia of parathyroid glands, elevated levels of immunoreactive parathyroid hormone (iI'TII)_ , skeletal resistance to the action of iPTli, deficient release of active vitamin D consequently defective intestinal calcium absorption are now known to be responsible for the bone disease in chronic renal failure. The mechanism responsible for some of the above are known while some are not yet clear.

The intake of elemental phosphorus approximates one gram per day. About 30% of this is excreted through the gastro-intestinal tract and *?0%* (3) or about 700mg/ day is excreted by the kidneys. Phosphate homeostasis is governed by parathyroid hormone (PTH) (l*i). Most of phosphate tubular reabsorption takes place in the proximal tubules (13) though some investigators have presented evidence suggesting distal reabso-ption (13)«

Early in renal failure, there is transient and possibly undetectable increase in serum phosphorus with each deterioration in renal function. This transient hyperphosphataemia would directly decrease the blood levels of ionized calcium (3,1^,15,16) which would then stimulate the parathyroid gland to release PTH. The latter decreases the

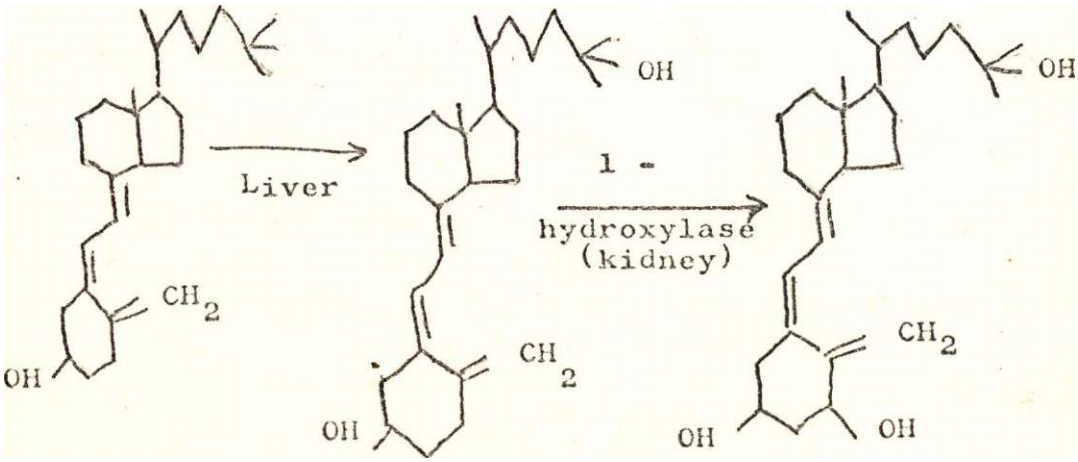
renal tubular reabsorption of phosphate with a return of both serum phosphorus and calcium levels to normal at th expense of elevated levels of blood PTH. As the g.lomeru lar filtration rate (GFR) falls, there is progressive increase in fractional excretion of phosphate (3.7) until the GFR falls to less than 30ml */uin* (l,3.6,l8) when frank hyperphosphataemia develops. The latter does not cause PTH release but indirectly stimulates parathyroid gland through hypocalcaemia.

There are other factors that contribute to the cause of hypocalcaemia and these include? the decrease in dietary calcium either because of anorexia in uraemia or prescribed low protein diet aitned at reducing hypera-zotaemia, acidosis and hyperphosphataemia; reduced intestinal calcium absorption which is usually present when the GFR is less than 50ml /mill (15*17)• The cause of calcium malabsorption was said by Stanbury et al (lj) to be due to specific intestinal abnormality caused by uraemic state* Decreased synthesis of 1, 25 $(OH)_{\circ}$ 0 by the diseased kidneys is responsible for the impaired calcium absorption from both the gut and renal tubules. Hyperphosphataemia per se has been reported by Slatopols (3) and acidosis ($18_{t}19$) to inhibit calcium absorption

in the gastro-intestinal tract. Acidosis also reduced renal tubular calcium reabsorption (20) leading to hypercalciuria. With the progressive fall in serum calcium, there is subsequent rise in PTH leading to high levels of circulating l'TH acting on bones but because of skeletal resistance (15) hypoc-alcaemia persists.

3.1 Metabolism of Vltamln JJ

The major sources of Vitamin D are skin and diet and the first step in its metabolism is in the liver where *25* - hydroxy vitamin D **(25** - OHDg) is formed® The latter is then metabolized to dihydroxycholecalciferol (l»25(0H)$_2$ D^) in the kidneys. The synthesis of 1,25 (Oil) ^ 13, requires an enzyme 1 - alpha hydroxylase (which is also present in the placenta during pregnancy).



$^{D}3$ °ƒ -OH ~D. 1,25, -(OH), L>$_3$

Metabolism of vitamin D,

X_t25 (OH) $_2$ D $_3$ is the active metabolite aisd acts on both kidney tubules and gut.

In chronic renal failure there is impaired synthesis of 1$_s$25 (OH) $_2$ D $_3$ partly because of the inhibitory effect of hyperphosphataemia on the renal 1 - alpha hydroxylase (2l) or .loss of renal mass (22). The low levels of 1,25 - (OH) $_{d.}$ D$_{v}$lead,-> also to skeletal resistance to $_j$ PTH causing hypocalcaeraia end markedly raised PTH causing osteitis fibrosa cystica. Poor absorption of calcium, that occurs in chronic renal failure is also due to low levels of 1,25

3.2. ACIDOSIS

Acidosis had been reported before as the major cause of bone dissolution (22) but this is now known not to be true because all patients with chronic renal failure have acidosis but not all of them have features of secondary hyperparathyroidism The latter however is a constant complication as the glomerular filtration rate falls to 30ml/min (2l) linked with diffuse hyper-plasia of parathyroid gland and markedly raised PTH causing osteoclastic type of bone resorption (osteitis fibrosa).

Because of the impaired vitamin metabolism and hypocalcaemia as explained =»bove, there is subsequent failure of bone mineralization characterizing osteomalacia of chronic renal failure.

AIMS OF THE STUDY

This study was undertaken to determine early biochemical and radiological changes that occur in patients with chronic renal failure as seci at KNH before and.during dialysis» And also to determine the effects ofs-

1* Duration

2. Age

3• Sex

$^{1}t_{e}$ Creatinine clearance

5» Serum bicarbonate

On:-

1» Clinical presentation

2. Inorganic phosphate

3* Serum calcium and

Radiology.

MATBRIALS AND METHODS

1» .Solection of Patients

Chronic renal failure patients attending renal clinic or admitted in medical wards were selected. Included also were those patients on dialysis. The ages were 15 years and aboveo

Patients who were on drugs known to affect bone metabolism like propranolol, anti-convulsants were excluded from the study$_t$ Also excluded were those with various bone diseases like multiple myeloma or acromegaly.

2• Bjochetn1ca1£va1ua11on•

Five mis of free flowing venous blood (no tourniquet) was drawn and from this serum blood urea nitrogen, calcium, inorganic phosphate, creatinine alkaline, phosphatase, and bicarbonate were determined using S>iA autoanalyser (R) • Twenty four hour urine collection was made and urinary creatinine determined by autoanalyser (R) and creatinine clearance (GFR) calculated by the following formular (using serum creatinine obtained above).

$$\frac{U \times V}{P}$$

Where U= Urinary Creatinine in mmol/1

V= Urine in the mis per 2-'t Mrs

P= Serum creatinine in mmol/1.

5• HpdAologj.c.a1 E;cam.ination

Patients were sent for X-ray of the hands, lumbar spine, pelvis and both femurs. Repeat radiographs- were taken after a period of 3 months for those patients who were still alive® All x-ray films wci'c reported by one radiologist.

k. CIjn;;cal Examination

The duration of illness was confirmed. This was taken as the interval between the point at which the patient was seen and the time that the first symptoms of renal disease were noticed by the patients, namelyJ oliguria, anuria, Polyuria, periorbital oedema, peripheral oedema or clinically confirmed episode of acute renal failure from which the patient recovered.

In the history a special attention was paidtto the symptoms of renal osteodystrophy„ These included bone pains, dxfficulty in walking and obvious fractures.

Following the history the patients were then subjected to thorough physical examinations. Particular attention was paid to the skeletal systems. Any deformity was looked for, and by gentle palpation tenderness was elicited along the vertebral bones, iliac crest and tibia.

5» Statistical analysis

For the statistical analysis the student "t" test was used to tost the significance of the differences or correlations. After computing the "t" values using the formula below, the significance (P) was obtained from the standard statistical tables,

11 > 11 $x_1 \sim x_2$

¥ $\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$

$(n_i + n_2$

where ^ refers to the means

n refers to the numbers and

s refers to the standard deviation.

• RESULTS

1«, Patients.

Of the 31 patients in the study 1?(54.8%) were males and *Ik* females (45.*2%*).

2. Ciin-ir.^ Presentation

Table 1

2.1 Clinical presentation of the 3-1 patients in chronic, renal failure

Presentation	Number	Percent
No symptoms and signs	4	12.9
Symptoms only	6	19<3
Signs o-ily	2	6.5
Symptoms and signs	19	61.3

Clinical renal osteodystrophy was taken to be present whenever bone tenderness and restricted joint movements were demonstrated (signs). By this criteria 21 of the 31 patients (67•7-») studied had clinical renal osteodystrophy, There were h patients of 31 patients *(1.2%)* with no symptoms and signs.

2•2 Symptoms:-

Major symptoms were of bone pains particularly on the back, around lumbar area and lower limbs. There were 27(27.1%) of 31 patients with cither symptoms only or signs only or symptoms and signs« 6 of these (19» had symptoms only while 19(Gl.3/5) had both symptoms and signs. No patient had pathological fractures.

2,3 Si t-;ns : -

Bone tenderness, on gentle palpation and restricted joint mo.ements, were found in 21 **(67**.7°') of 31 patients and 2 of 31 (6.'i?0 had signs only without symptoms. Most of the .signs *were* found in the long bones, lumbar vertebrae and pelvic bones.

TABLE 2

Sex distributlon of the priisculatlon in the 3-1 patients in chronic renal failure

-jex	No symptoms arid signs (1)	Symptoms only (2)	Signs only (3)	Symptoms and signs U)	Heixal Osteo-dystrophy (signs only or symptoms and signs) (3+'<)
>iale	1	*k*	1	11	12
emale	3	*O*	1	ů	9

Out of 31 patients, 17 (5[1]L.8%) were males and 14 (!i5o?%) females. Of the 17 male patients seen 12 (70«6'**o**) had clinical renal osteodystrophy (signs alone ox" symptoms and signs) as compared to {)(6k«3/o) females. Tlxre was however no difference between the two sexes in clinical presentation,

TABLE 3

2.5 distribution of the Pros ontati on'

Ago Years	No Symptoms and signs.	Symptoms only	C1inica1 rena1 Osteodys trophy
10 - 20	0	1	2 (66.7")
21 - 30	1	j)	10. (71.)
31 - -i0	1	O	5 (62.5-)
'll - 50	2	0	*!i* (66.7?J)

Clinical renal osteodystrophy was demonstrated amongst all age groups studied. There was no significant difference (PJ>.50) between 30 years of age and those below in clinical, renal osteodystrophy.

Table 4

[2] «• 6 Effeet ofjuration on clinical renal osteodystrophy

Presentation	Duration (months)
No symptoms and signs (1)	17,20,24,10 Mean 17-75 + 5.91
Symptoms only	'18,1,3,39,7, 18 Mean 19.3 + 19.8
Clinical renal osteodystrophy (3)	48,24,**60**,24,1*1,36,24, 37,38,38,48,29,48,36, 53,24,48,23,60,20, Mean = 36*5 + 13.9

Those patients with clinical rer.aV oftteodystto\ilvy had mean duration of illness of 36.5 + 13.9 months. There was statistical significant correlation in duration of illness between those patients with clinical renal osteodystrophy and those without (1+2).

Patients who presented with no symptoms and signs had mean duration of illness of 1?.-75 ± 5.91 months and those who had symptoms only had mean duration of illness of 19.3+19.8 months.

Duration of illness therefore plays an important factor in the development of clinical renal osteodystrophy.

3• Bjoc1;em±ca1 rcnaI osteocly,s1.rophy

Biochemical renal osteociystrophy was said to be present whenever there was raised serum alkaline phosphatase (normal range 30 - 115mmol/L) together with low serum calcium (normal range 2.25 - 2.50 mmol/l) and high inorganic phosphate (normal range 0.8l - 1.36 mmol/l).

Table 5

3.1 Table of presentation end mean alkaline phosphatase

Presentation	Mean Alkaline Phosphatase mmol/l
No symptoms and signs	**80.8 + 17.04**
Symptoms only	**79.9 t 20d2**
Clinical renal osteodystrophy	**180 + 85.4**

Patients with clinical rsnal osteodystrophy had raised mean serum alkaline phosphatase i.e. 180 + 85.4 mmol/l. There was significant statistical correlation between clinical presentation and biochemical renal osteodystr-ophy. (P<C«00l)

Table 6

3 • 2 Table of ^'iration and moan soruni alkaline phosphatasc

Duration (months)	Mean serum alkaline phosphatase (mmol/l)
0 - 1 0	77.5 + 16.4
11 - 20	110® 7 + 31.8
21 - 30	174.0 + 21.5
31 - 40	187.6 + 12.7
41 - 50	164.2 + 7.8
^ 5 1	218cO + 5.1

Patients who had been ill fcr a period of more than 21 months lu.d markedly raised alkaline phosphatase* The table shows that there is steady rise uf serum alkaline phosphatase as the compromised renal function persists signifying bone involvement during chronic renal failure.

3.3 The effect of duration . scrun calcium, so run inor.^anic phosphate nor^r' al[1]:;: lj ne ^•nrpliaT.^sc, serum iiUTa', creatinine clearance and scrim bicarbonate on presentation.

Table 7

Table of the ••••• (:;) ami standard deviation (S.D).

P rcsontation	'Juration (months) Vw Cans	S.D	5erum Ca1ciim M	S.D	S erum Inorgani c Phosphat.e M	S.D	S erum Alkai in Phospli a tase K	S .D	S erum 3icar bonatc K	S.D	S erum V	S.D	Great inine Clear ance >i. i	0. ij
Iso symptoms *an-1* signs	17 (Po	5.9	1.	0.19	3.34	1.53	80.75	17.0	17.8	11.3	35.5'	20.1	5.9	8.7
—v^aaomi s or. 1 v	19.3	19.3	1 CO /	0.28	1.81	0c'i	79.9	20.2	17.7	9o5	34.7	19.3	7-2	9.1
01iaicnl r . • 1. 0,• teodyst- Vo] -j 1 i y	36.5	15.9	1.46	n 0 w » - /	J » S>u	» <- j	I82 „ 1i	39.1	17.7	6.6	39.1	17.3	10.2S	1 r i L^ » ±
	+ 16 .1i .Oi^lTc.025		+ 1 « vj P<0.03		t 1o30 .25<1>< .05		+ .-'{0 P<c ..001		+ 5.0 P-o50		1 31.3 P= .5G		+ .68 P.^012	

Table 8

Tab3 e of r.ieans anc1 standard deviat.1on of aj.ka.1ine phosphatase, inorpan1c pliosphate, serum caIcIT;m> duration of illness and vhrir correlation with creatin1necIearance.

Creatinine Clearance (MlsAu.n)	Alkaline Phosphatase (mmol/l)	Inorganic Phosphate (mmmol/l)	Serum Calcium (mmol/l)	Duration (months)
0 - 1 0	145.93196.5	3.62+1.3	1.58+0.36	29.V7+II.4
11 ~ 20	155.0+89.5	**2.08+0.55**	**,1.6+0.2?**	28.2+10.12
21 - 50	**126**.5**+18,**5	**2.25+0.56**	**1.76+0.085**	35.5+17.5
31 - ’i0	140.5+16.5	1.62+0.14	**1.73+0.32**	23.5+0.5
	P <.01	P <.012	P <.04	P.10

All the patients studied had creatinine clearance below 40ml/min. There was rise in mean alkaline phosphatase, inox^ganic phosphate with the fall of glomerular filtration rate.

There was significant statistical cox-relation between creatinine clearance and alkaline phosphatase (P = <<£.012)$_t$ scrum calcium (P -

There was no correlation between creatinine clearance and duration of illness (P>.50).

Is the age distribution of the 31 patients studied in chronic renal failure. The histogram shows that age group studied ranged between 15 years and 50 years. Host of the patients (90.3%) studied were above 20 years of age with a peak age between 20 years and 30 years (i.e. ᶻi5*2?u of the 31 patients).

Shows age distribution of clinical presentation of 51 patients studied. The histogram shows that clinical renal osteodystrophy was evenly distributed amongst all the age groupsₑ

Shows relationship between duration of illness and mean serum alkaline phosphatase. The histogram shows that there is steady rise in alkaline phosphatase with prolongation of life of patients in chronic renal failure. There is statistical significant correlation between alkaline phosphatase and duration of illness (P = ^/.OOl) .

Fig.'i Shows relationship between fall in creatinine clearance on mean serum alkaline phosphatase. The histogram shows that all the patients studied had their creatinine clearance below 40mls/min. There was statistical significant correlation between creatinine clearance and alkaline phosphatase (P = .

Fig.5 Shows relationship between creatinine clearance and serum inorganic phosphate. The histogram shows that as the creatinine clearance falls to and below 40mls/min» there is rise in serum inorganic phosphate. There is statistical, significant correlation (P = d.e012).

Fig.6 Shows relationship between creatinine clearance and serum calcium. There is fall in serum calcium with fall in creatinine clearance. The fall in creatinine clearance correlates statistically with serum calcium (p = ^cxo.

FIG. 1 AGE DISTRIBUTION

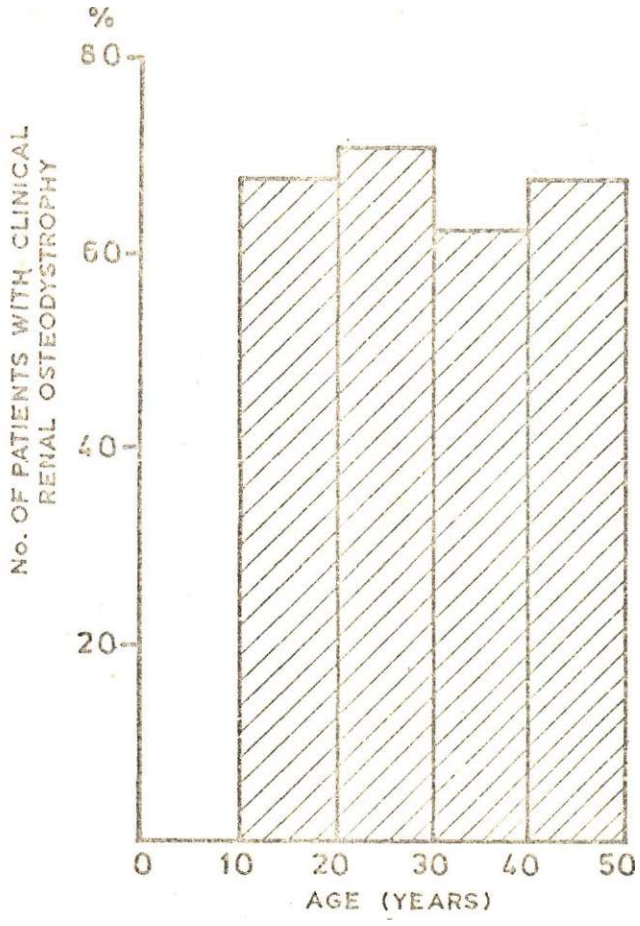
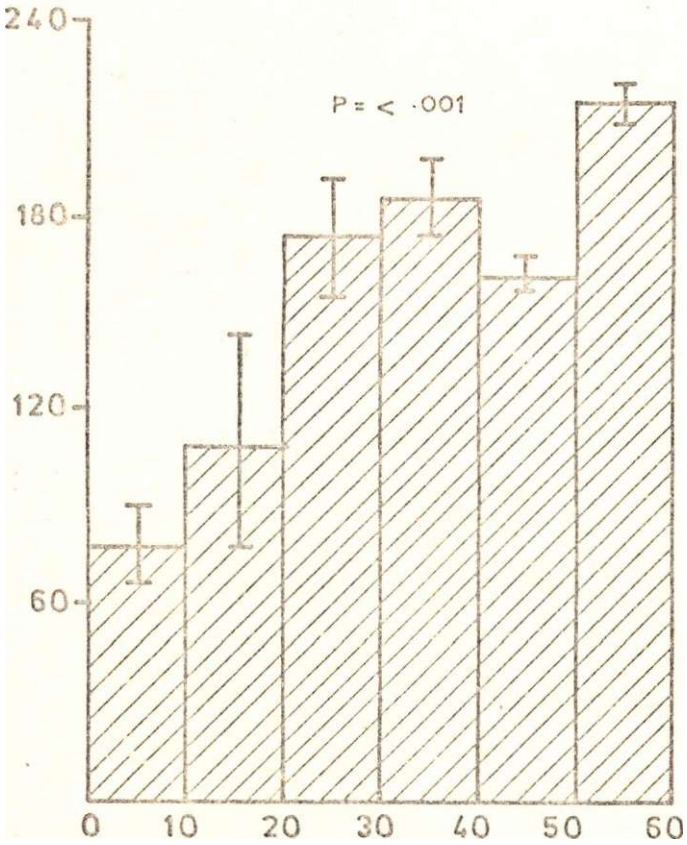

%
80
60
40
20
No. OF PATIENTS WITH CLINICAL RENAL OSTEODYSTROPHY
0
10
20
30
40
50
AGE (YEARS)

FIG. 3 EFFECT OF DURATION ON SERU
ALKALINE PHOSPHATASE



MEANS OF ALKALINE PHOSPHATASE AND CREATININE CLEARANCE

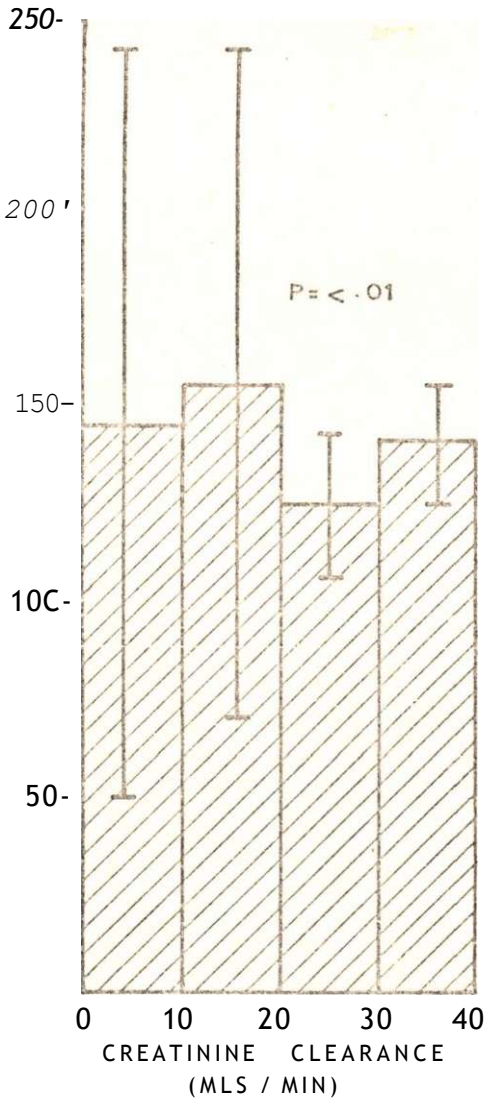


FIG. 5 MEANS OF INORGANIC PHOSPHATE AND CREATININE CLEARANCE

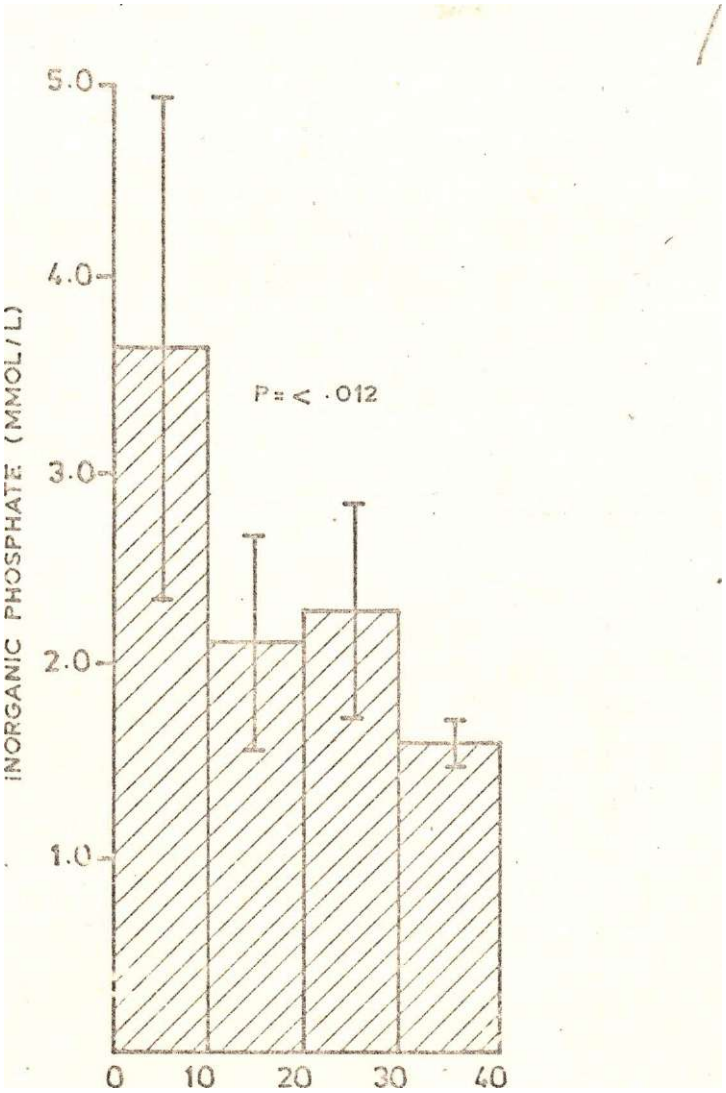
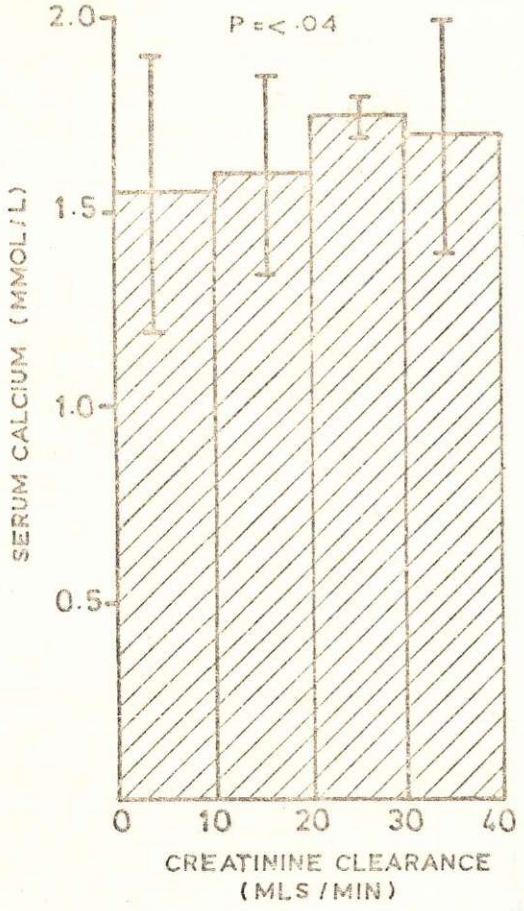


FIG. 6 MEANS OF SERUM CALCIUM WITH CREATININE CLEARANCE



Renal osteodystrophy as first described by Clement Lucas in 1883 (1) and later reported by Fletcher in 1911 (5) is a bono disease of chronic renal failure that mainly affects the spine, long bones and pelvis. Most of the patients have bone pains (22,23,24) tenderness and proxima rauscle weakness. All the patients in this study who had clinical renal osteodystrophy had pains in the lower limbs, pelvis and back particularly on exercise, which is similar* to the findings of Kanis (22) . None of the patients complained of pain in the upper limbs. The frequency with which Osteomalacia (part of renal osteodystrophy) causcs symptoms is very variable i.e. in Oxford H'enal Unit only 10~20?o had symptoms while in Newcastle Renal Unit where the incidence of osteomalacia is greater (25) the symptoms appeared to be more frequent. In this study group it was not possible to categorize the most frequent form of bone lesion because no histological examination was performed, but 67*7% had clinical renal o steodystrophy«. The latter does not occur only in osteomalacia but also in osteitis fibrosa cystica (23)« Fracture particularly of the pelvis and femoral neck does occur with variable frequency but is more common

in dialysis centres which tend to have high prevalence of osteomalacia **(22).** None of the studied patients had fractures both clinically and or radiologically.

The mean creatinine clearance (GFR) was 10_f29mls/min which is much better than other studies (26) in which patients had poorer renal functions and must be maintained 011 dialysis tending to have severe forms of renal osteodystr-ophy. Dialysis was not used routinely in any of the patients studied even though their renal functions were very poor. This was so because of the financial restri-ction of chronic dialysis in the hospital. Cost benefit disqualified most of them if not all the patients who otherwise could have been put on Continuous Ambulatory Peritoneal Dialysis (CAPD).

Before the start of dialysis, osteitis fibrosa affects *80%* of patients *in* end stage renal failure (ESRF) histologically, ***20%*** radiologically and a few percent symptomatically **(27).** ^{A}H these tend to regress only when both calcium and phosphate levels are controlled with the onset of dialysis. Osteomalacia is on the other hand very uncommon before the start of dialysis.

Some patients develop more severe bone disease than others and some develop osteomalacia while others osteitis fibrosa. The reason for thece differences is not yet known«

Whereas osteomalacia osteodystrophy is frequent in Europe, it is reported less often in United States (28) indicating some geographical variation. Apart from environmental factors ^23)^genetic factors (29) do determine whether or not a given state of Vitamin D deficiency or resistance results in osteomalacia or not. In this study it was not possible to determine the predominant bone disease. About 50% of patients in terminal renal failure of less than one (12 months) year's duration have normal bone biopsies (25,29) though they have both clinical and biochemical renal osteodystrophy. The hormone (PTH) levels are higher the longer the duration or the greater the severity of the renal failure (15)» The exact point at which chronic renal failure stcirts is difficult to determine because some patients have been living faix-ly normally with impaired rer.al function but present only when, due to an added, insult on the failing kidneys that,they develop overt and symptomatic chronic renal failure (CRF).

Sometimes a patient may go sti~aight from an episode of acute renal failure i.e. rapidly progressive glomerulonephritis to chronic renal failure. In this study the mean duration of illness in patients with clinical renal osteodystrophy was 36.5 ± 13•9 months and there was marked significant statistical correlation (»01*£.P <1^.025) • There was also significant correlation (Pc^.,025) between dtiration of illness and biochemical renal osteodystrophy (rise in alkaline phosphatase lOO + 85.^ mmol/1 normal range 30 - 11.5 mmol/l).

In this study most of the patients were not on regular dialysis and thei'efore did net live long enough to manifest radiological changes. None of the patients studied had any radiological changes with the mean duration of illness of 36.5 ± [1]3«9 months.

It has been reported elsewhere by certain authors that females are more liable to skeletal diseas.e (23) in end stag~ renal failure. The reason fo$_s$r this is not clear though in this study there was no correlation or difference between'the two sexes (P>».50). This was true for clinical, biochemical or radiological renal osteodystrophy.

Metabolic acidosis is characteristic of chronic renal failure and in this study the mean serum bicarbonate of 17„7mmol/l was found in patients with clinical renal osteodystrophy* There was no statistical correlation between clinical presentation and acidosis (P j>.50>. There is no evidence to indicate whether or not systemic acidosis interferes with initiation of mineralization in the osteid bone or not (l5)« This is because correction of the acidosis does not influence renal osteodystrophy and yet appropriate treatment with vitamin li will cure azotaemic rickets and osteomalacia even when acidosis is left untreated» Cochran and Nordin (24) have however shown that acidosis does affect bone mineralizatio firstly because of its hypocalcaemic effect and secondly through its metabolic "hypophosphataemia" which occtirs with fall in pH»

Phosphate retention plays the major role in the development of Secondary hyperparathyroidism in chronic renal failure by inducing changes in ionized calcium (30). It is this latter cation that affects the secretion of PTH, As frank hyperphosphataemia occurs, with the falling creatinine clearance, (lB)

secondary hyperparatliyroidistn develops and as in this study the mean inorganic phosphate was 3«3& ± 1.25 mrnol per litre (normal range 0.8l - 1.36 mmol/l) showing marked significant statistical correlation (• 25*^-P 5) with clinical renal osteodystrophy. Hyperphosphataeraia does also inhibit 1,25 (OH) production (14) leading to impaired intestinal calcium absorption and subsequent hypocalcaemia* In this study the mean serum calcium was 1.46 ± 0,2? mmol/l (normal values 2.25 - 2.50 mmol/l) showing significant statistical correlation (P^Ol) with clinical renal osteodystrophy. Apart from hypocalcaemia contributing to PTH hypersecretion, there is also impaired renal degredation *ilk)* leading to its elevated levels in chronic renal failure. Even though it was not possible to estimate itnrnunoroactive PTH in these patients it can be assumed that with such markedly raised irorganic phosphate, low calcium and vei~y poor renal function its level must have been raised leading to secondary hyperparathyroidism. The symptoms and signs specific to this included clouded mentation which could also be due to uraemia itself, bone pain and tenderness# There was also marked muscle weakness and atrophy in these patients with chronic renal failure.

2 *J*

It is now well known that mature collagen fibres form nucleation scaffoldings for the precipitation of calcium phosphate salts (_>1). The specific, orientation of collagen fibres within the bone matrix together with their crystalline phase gives the bone its structural property arid tensile strength«

Co3.1agen molecule is a polymer of tripeptides. Hydroxyproline constitutes *lk%* of the amino acid residues in collagen. It is derived within the osteoblast by hydroxylation of amino acid, proline, during collagen biosjTithesis. It is released into circulation as hydroxyproline during bone collagen degredation. It is not reutilized and therefore either degrated in the liver or excreted normally in the urine (52). Th*» cellular phase is essential for day to day formation, remodeling and bone resorption, the process which condition and maintain skeletal intergrity. The osteoblasts are important in this respect. During mineralization, there is an elevation of "bone" alkaline phosphatase which is heat labile unlike liver, intestinal and placenta alkaline phosphatase which are heat stable.

During mineralization the osteoblasts get buried in the bone matrix and become osteocytes and the latter release alkaline phosphatase.

Apart from serum or urine hydroxyproline which is a more sensitive measure of bone resorption in chronic renal

failure than radiological cha*Ti*-ges^
s

alkaline phosphatase tend *fLo* be raised in patients with bone disease (30)® In study done by Ingham et al (23), it was found to be elevated in all patients«

Although a definite diagnosis of disturbed bone mineralization is made by bore histology, elevated alkaline phosphatase may be the first indication of rena osteodystrophy (10,27) and therefore is an important biochemical parameter in making its diagnosis (33)• It can also be used to determine response to therapy (3'i) by its decline. In this study 18 (51.1%) of 31 patients had raised alkaline phosphatase. There was significant statistical correlation between clinical and biochemical (raiseu alkaline phosphatase) renal osteodystrophy (P^il.001) . Isoenzymes were not studied but it is certain that raised alkaline phosphatase was from bono and not liver because these patients had no gastrointestinal problems and also where such study has been performed (3) it vas found to be skeletal origin.

CONCLUSION

Renal osteodystrophy is a known complication of chronic renal failure and tends to occur more commonly in patients on chronic dialysis. It was seen in some of our patients attending renal clinic.

In Kenyatta National Hospital, patients with chronic renal failure present late, and usually as acute on chronic when very little can be dene to improve their compromised renal functions. The longer the duration of illness the severer the bone disease. In this study it was found to be in keeping with other studies elsewhere. It therefore shows that duration is an important factor.

In this hospital renal disease and particularly chronic renal failure tends to occur more commonly in the early age groups (i.e. less than kO years which is the reverse in developed countries) than old ones.

All patients studied were aged below 50 years yet in developed countries chronic renal failure is commonly seen above '10 years.

Azotaemic bone disease is known to occur more frequently in children than adults. This study however shows that, in Kenyatta National Hospital, renal osteodystrophy is common also in adults. Similar finding has been reported by other authors from developed countries, as a major problem affecting all age groups.

Some authors have reported women as being more commonly affected but this was not revealed in in our patients.

Taking creatinine clearance as a determinant of deteriorating renal function, it was found that with the falling glomerular filtration rate, thei'e is rise in incidence c-f both clinical and biochemical renal osteodystrophy.

Phosphate retention with the falling renal function is an important factor in the initiation of secondary hyperparathyroidism.

This finding has also boon reported by other authors. In the management of azotaemic renal disease, lowering of scrum inorganic phosphate is of vital importance.

The causes of hypocalcemia are multifactorial and therefore the use of calcium supplements without correction of hyperpliosphataemia may be of no benifit.

Serum alkaline phosphatase is an important indicator of renal osteodystrophy. It has beer, used and confirmed histologically by certain authors elsewhere. In centres where biochemical estimation of serum or urinary hydroxyproline and or iinmuiioreactivc parathyroid hormone (iPTIl) is not possible it can be used alone to make a diagnosis of azotaemic bone disease.

Radiological changes, though very common in children (and adults as reported elsewhere:) wore not seen in this study mainly because of age group studied and short duration of illness

Patients with chronic renal failure as seen at Kenyatta National Hospital do not live long enough to show radiological bone changes. It is therefore possible that these changes will be seen in our adult patients when intermittent chronic haemo-dialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD) is started.

H K F £ R £ N C E S

1, Liu, S.1I. and Chu, H.I$_0$ (l9'i3) Studies calcium and phosj>horus metabolism with special reference to pathogenesis and effects of dehydrotachysterol and 1ron« Medicine, Baltimore 23; 103 (23^)

2. Hanley D.A. Medical clinics of North America Vols 62 No. 6 (1978).

3 Slatopolsky L, Rutherford B., Ruthei'ford E., Hruska K; Martin Kj Klahr, S. How important is phosphate in the pathogenesis of renal osteodystrophy: Arch. Intern. Med. Vol. 138 (1978)«,

h. Lucas R.C. (1883) Form of late rickets associated with Albuminuria; rickets of Adolescents: Lancet Vol. 1 (1883) 993-993.

Fletcher II.M. (l911)
Proc. R. Soc. Med. k\ 95

6. Parsons, L.G. (1927)
Arch. Mis. Childh. 2^,1.

7. Stanbury S.\,^{r}. Azotaemic renal osteodystropliy Br. Med. Bull. 11:1, 57-60 (.1957).

8* Albright, P., and Brake, T.G. and Sulkowitch, 11.v. (1937).

9e Park, E.A. & Elliot, M.M (193?) 3rennciaann, J. ed. Practice of Paediatrics, vol. 3 Chapter 29*

10. Ellis, II.A. and Peart K.M, Azotaernic renal osteodystrophy. Aquantitative study on Iliac bone. J. Clin. Path. 26: 83 (1973)»

11. Abdulla, M.S$ Editorial. East Afr. Med. J. 58: 309 (1981).

12. Roger Gabriel. Post graduate Nephrology Edition.

13» Strieker G et ale, Micropuncture study of inorganic phosphate excretion in the rat. J. Clin. Inv. 431 1396 - 1607 (1964).

Ik, Hassry S.G, Ritz Ej (1978) The Pathogenesis secondary hyperparathyroidism in renal failure. Arch. Int. Med. Vol. 138: 853 - 857,

15o Stanbury, S.W. Done Disease in uraemia Am. J. of Med. *kk: 7lk - 72k* **(1968)**

16. Founder A et al. Prevention and medical treatment of hyperparathyroidism secondary to renal failure in Adults. Adr. in Nephrology Vol. 11: 2k1 - 271 (1982).

17. Curbun J.w , Loppel M«H» Drichraan A.S. et alt Study of intestinal absorption of calcium in patients with renal failure* Kidney Int. 3"'2,Gk - 272? (1973).

18. Eyanson J.M. (i960) The response to the infusion of parathyroid extract in hypocal- caemia state; Clin. £>ci . 31:

19• Litzow, J.Rf Lentann, J. and Lennon, C.J. The effect of acidosis on calcium balance in patients with chronic renal disease. *J* Clin. Inv; 46: 280, (1967).

20. Leniann, J., Litzow, J.R. and Lennon, C.J. The effect of chronic acid loads in normal mailt further evidence for the participation of bone mineral in the defense against chronic acidosis. J. Clin, lav; *k^i* **1608 (1967).**

21. Stanbury S.U[T]; Lumb, G.A., Hawer E.G. Osteodystrophy developing spontaneously in the course of chronic renal failure. Arch, Int. J^ed. *1969; 12h: 27'i* - 81.

22. K^nis J,A. Osteomalacia and chronic renal failure. J. Clin, I'ath; 3-'i: 1295 - 1307 (l9Bl).

Inghar.i J.P., Kleerekoper, M.j Stewart, S.H.: Symptomatic skeleta Disease in non-terminal renal failure med. J. Aust, 197^ 1* 873 - 87C.

Cochran, M.f Nordin, 3.E.C; Role of acidosis in renal osteomalacia. Br, Med. J« .1969, 2. 276 - 279.

Ellis II.A. et al. Histopatliology of renal ost-eodystrophy with particular reference to the effects of l-alj^ha-hydroxyvitamin D in patients treated by long term haemodialysis. Clin. Endocrin, (0xf.) 19775 7' 31-8.

Jebsen, H.R., Tenekhoff, H,, lionet, J.Ct, Natural history of uraemic polyneuropathy and effect of dialysis. N. Eng. J. Med. 277: 327, 19^7•

Hurler A.R. 1978 Editorial Progress in clinical Medicine.

Lumb G.A. Mower, E»B, The apparent Vitamin U resistance of chronic renal failure Am. J. Med. 50: >121, 1971.

Ingham J.l'., Stewart J.H. and 1'osens. (1973)

Quantitative skeletal histology in untreated end-stage renal failure. Br. Ned. J. 2: 7'i5.

30. Varghcsc, Moorhead, WiHis 1973
Plasma calcium and magnesium fractions in chronic renal failure patients on Gaetnodialysis. Lancet 2; 985 - 988 1973*

31. Glimchur, M.J. and Krane, S.N. The Organization and structure of bone mechanisms of calcification. In Gould, B.S. (ed,) Vol. 2B. Academic Press London 1968 P„ 67*

32. Avioli, L.V,, Sharp; C. and Birge(S.J., Catabolism of free hydroxyproline in chronic uraemia. Am. J. Physiol. 217: 536, 1964.

33c Eric J.W.; Linear Decline in Scrum Alkaline Phosphatase activity during treatment of renal osteodystrophy Br, Mod. J. Vol. **286 (1983)**

3'l$_0$ Kanis J.A.; Cundy „T. ; Earnshaw M. et al Treatment of renal bone Disease with l-alpha-hydroxylated derivatives of vitamin Q. J.mod. 1979; 48 - 322.