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

BY

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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.

Signed: Br. J.H. Swao (candidate)

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

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ACKNOWLEDGMENTS

I wish to express many thanks to all who contributed to this dissertation.

First of all I am greatly indebted to my supervisor Dr. L.S. Otieno for his excellent guidance, support, encouragement and useful criticism during the study.

I am thankful to Dr. P.J. Ojv.ang of the Department of Pathology (Chemical) for support and encouragement. I would also like to take this opportunity of thanking hr. W. Gemert of Clinical Research Centre for statistical analysis and Mrs. Margaret Kamau for typing the manuscript.

I am also thankful to all staff of both renal clinic and medical wards for assistance accorded to me during this study.

I wish to express my gratitude to my wife, Amondi, and daughters for their understanding and encouragement during the difficult days when I was carrying out the study.
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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 age groups studied (15 to 50 years). Pain in the lumbar and long bones were among the most frequent and consistent early complaints. Serial skeletal x-rays, 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 (.01>P<.025). Biochemical renal osteodystrophy, taken as raised serum alkaline phosphatase (mean 182.4 ± 39.1 mmol/l) and serum inorganic phosphate (mean 3.36 ± 1.25 mmol/l), was found in 18 (58.1%) of 31 patients. There was significant correlation between creatinine clearance (mean 10.29 ± 15.1 ml/min) and biochemical renal osteodystrophy (P<.01).
INTRODUCTION AND REVIEW 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 (1973) (1). 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 forms: 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)).

2. Historical background of renal osteodystrophy

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 rickets" or these terms were used to describe it (7). At that time it was however obvious that dietary deficiency of vitamin D 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 occurring 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 bone disease was very rare as most patients used to die in the early stages of chronic renal failure (10) a situation pertaining in Kenya now. Both maintenance haemodialysis and peritoneal dialysis were successfully performed in 1970's (11, 12) though with restricted application. Either of the two technique became widely used in 1960'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 past few years concerning the understanding of pathophysiology of renal osteodystrophy.

Pathophysiology and pathogenesis of renal osteodystrophy:

The mechanism responsible for the development of renal osteodystrophy in patients with chronic renal disease are multifactorial and poorly understood (1,2).
The manifestation of deranged mineral metabolism in uraemia include hypocalcaemia, hyperphosphataemia, hyperplasia of parathyroid glands, elevated levels of immunoreactive parathyroid hormone (PTH), skeletal resistance to the action of iPTH, 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 20% (3) or about 700mg/day is excreted by the kidneys. Phosphate homeostasis is governed by parathyroid hormone (PTH) (1*1). Most of phosphate tubular reabsorption takes place in the proximal tubules (13) though some investigators have presented evidence suggesting distal reabsorption (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 (3,1^1,15,16) 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 the expense of elevated levels of blood PTH. As the glomerular filtration rate (GFR) falls, there is progressive increase in fractional excretion of phosphate (3.7) until the GFR falls to less than 30ml/min (1,3,6,18) 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 aimed at reducing hyperazotaemia, acidosis and hyperphosphataemia; reduced intestinal calcium absorption which is usually present when the GFR is less than 50ml/min (15,17). The cause of calcium malabsorption was said by Stanbury et al. (1) to be due to specific intestinal abnormality caused by uraemic state. Decreased synthesis of 1, 25 (OH)₂O 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 (18,19) 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 1' TH acting on bones but because of skeletal resistance (15) hypoc-alcaemia persists.

3.1 Metabolism of Vitamin D

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 (125(OH)2 D3) in the kidneys. The synthesis of 1,25 (OIl)3 requires an enzyme 1 - alpha hydroxylase (which is also present in the placenta during pregnancy).
\( \text{X}_{25} \) (OH) D is the active metabolite and acts on both kidney tubules and gut.

In chronic renal failure there is impaired synthesis of \( \text{X}_{25} \) (OH) D partly because of the inhibitory effect of hyperphosphataemia on the renal 1-alpha hydroxylase (21) or loss of renal mass (22). The low levels of 1,25-D lead to skeletal resistance to PTH causing hypocalcaemia and 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 (21) linked with diffuse hyperplasia 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 above, 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 seen at KNH before and during dialysis. And also to determine the effects of:

1. Duration
2. Age
3. Sex
4. Creatinine clearance
5. Serum bicarbonate

On:-

1. Clinical presentation
2. Inorganic phosphate
MATERIALS AND METHODS

1. Selection 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 above.

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

2. Biochemical Evaluation

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 SxIA autoanalyser (R). Twenty four hour urine collection was made and urinary creatinine determined by autoanalyser (R) and creatinine clearance (GFR) calculated by the following formula (using serum creatinine obtained above).

\[
\frac{U \times V}{P} \text{ Where } U = \text{ Urinary Creatinine in mmol/l, } \\
V = \text{ Urine in the mis per 24t Mrs, } \\
P = \text{ Serum creatinine in mmol/l.}
\]
5. **Haematological Examination**

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 were reported by one radiologist.

k. **Clinical 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, namely 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 paid to the symptoms of renal osteodystrophy. These included bone pains, difficulty 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.
Statistical analysis

For the statistical analysis the student "t" test was used to test 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,

\[ t = \frac{X_1 - X_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \]

where \( \bar{x} \) 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, 17 (54.8%) were males and 14 females (45.2%).

2. Clinical Presentation

Table 1

2.1 Clinical presentation of the 31 patients in chronic renal failure

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms and signs</td>
<td>4</td>
<td>12.9</td>
</tr>
<tr>
<td>Symptoms only</td>
<td>6</td>
<td>19.3</td>
</tr>
<tr>
<td>Signs only</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Symptoms and signs</td>
<td>19</td>
<td>61.3</td>
</tr>
</tbody>
</table>
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 10 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 either symptoms only or signs only or symptoms and signs. 6 of these (19%) had symptoms only while 19 (61.3%) had both symptoms and signs. No patient had pathological fractures.

2.3 Signs:

Bone tenderness, on gentle palpation and restricted joint movements, were found in 21 (67.7%) of 31 patients and 2 of 31 (6.5%) had signs only without symptoms. Most of the signs were found in the long bones, lumbar vertebrae and pelvic bones.
### TABLE 2

Sex distribution of the praisculation in the 31 patients in chronic renal failure

<table>
<thead>
<tr>
<th>Sex</th>
<th>No symptoms and signs (1)</th>
<th>Symptoms only (2)</th>
<th>Signs only (3)</th>
<th>Symptoms and signs U</th>
<th>Heixal Osteodystrophy (signs only or symptoms and signs) (3+)&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1</td>
<td>k</td>
<td>1</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Out of 31 patients, 17 (51.8%) were males and 14 (48.2%) females. Of the 17 male patients seen 12 (70.6%) had clinical renal osteodystrophy (signs alone or symptoms and signs) as compared to 6 (36.3%) females. There was however no difference between the two sexes in clinical presentation.

### TABLE 3

2.5 distribution of the presentation

<table>
<thead>
<tr>
<th>Ago Years</th>
<th>No Symptoms and signs</th>
<th>Symptoms only</th>
<th>Clinical renal Osteodysrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 20</td>
<td>0</td>
<td>1</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>21 - 30</td>
<td>1</td>
<td>j</td>
<td>10. (71.7)</td>
</tr>
<tr>
<td>31 - 40</td>
<td>1</td>
<td>0</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>41 - 50</td>
<td>2</td>
<td>0</td>
<td>'i (66.7%)</td>
</tr>
</tbody>
</table>
Clinical renal osteodystrophy was demonstrated amongst all age groups studied. There was no significant difference (P > .50) between 30 years of age and those below in clinical, renal osteodystrophy.

Table 4

Effect of duration on clinical renal osteodystrophy

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms and signs (1)</td>
<td>17,20,24,10</td>
</tr>
<tr>
<td></td>
<td>Mean 17-75 ± 5.91</td>
</tr>
<tr>
<td>Symptoms only (2)</td>
<td>'18,1,3,39,7,18</td>
</tr>
<tr>
<td></td>
<td>Mean 19.3 ± 19.8</td>
</tr>
<tr>
<td>Clinical renal osteodystrophy (3)</td>
<td>48,24,60,24,1*1,36,24</td>
</tr>
<tr>
<td></td>
<td>37,38,38,48,29,48,36</td>
</tr>
<tr>
<td></td>
<td>53,24,48,23,60,20</td>
</tr>
<tr>
<td></td>
<td>Mean = 36*5 ± 13.9</td>
</tr>
</tbody>
</table>

Those patients with clinical renal osteodystrophy 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 17.75 ± 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.
Biochemical renal osteocystrophy was said to be present whenever there was raised serum alkaline phosphatase (normal range 30 - 115 mmol/L) together with low serum calcium (normal range 2.25 - 2.50 mmol/l) and high inorganic phosphate (normal range 0.81 - 1.36 mmol/l).

Table 5

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Mean Alkaline Phosphatase mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms and signs</td>
<td>80.8 ± 17.04</td>
</tr>
<tr>
<td>Symptoms only</td>
<td>79.9 ± 20.42</td>
</tr>
<tr>
<td>Clinical renal osteodystrophy</td>
<td>180 ± 85.4</td>
</tr>
</tbody>
</table>

Patients with clinical renal 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 osteodystrophy. (P<0.001)
Table 6

3.2 Table of **duration** and moan soroni alkaline phosphatasC

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>Mean serum alkaline phosphatase (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>77.5 + 16.4</td>
</tr>
<tr>
<td>11 - 20</td>
<td>110.7 + 31.8</td>
</tr>
<tr>
<td>21 - 30</td>
<td>174.0 + 21.5</td>
</tr>
<tr>
<td>31 - 40</td>
<td>187.6 + 12.7</td>
</tr>
<tr>
<td>41 - 50</td>
<td>164.2 + 7.8</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>218.0 + 5.1</td>
</tr>
</tbody>
</table>

Patients who had been ill for a period of more than 21 months had markedly raised alkaline phosphatase* The table shows that there is steady rise of serum alkaline phosphatase as the compromised renal function persists signifying bone involvement during chronic renal failure.
3.3 The effect of duration. serum calcium, serum inorganic phosphate, serum bicarbonate, creatinine clearance and serum bicarbonate on presentation.

Table 7
Table of the mean and standard deviation (S.D).

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Duration (months)</th>
<th>Serum Calcium</th>
<th>Serum Inorganic Phosphate</th>
<th>Serum Alkaline Phosphatase</th>
<th>Serum 3icarbonate K</th>
<th>Serum Uric Acid</th>
<th>Great Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iso symptoms and signs</td>
<td>20</td>
<td>1.7</td>
<td>0.19</td>
<td>3.34</td>
<td>1.53</td>
<td>80.75</td>
<td>17.0</td>
</tr>
<tr>
<td>19.3</td>
<td>19.3</td>
<td>0.28</td>
<td>1.81</td>
<td>0.01</td>
<td>79.9</td>
<td>20.2</td>
<td>17.7</td>
</tr>
<tr>
<td>36.5</td>
<td>15.9</td>
<td>1.46</td>
<td>0.00</td>
<td>39.1</td>
<td>17.7</td>
<td>6.6</td>
<td>39.1</td>
</tr>
</tbody>
</table>

*P<0.05*
Table 8

Tab3e of r.ieans ancl standard deviat.1on of aj.kaline phosphatase, inorpanlc pliosphate, serum calcIT; m> duration of illness and vhrir correlation with creatin1neclearance.

<table>
<thead>
<tr>
<th>Creatinine Clearance (MlsAu.n)</th>
<th>Alkaline Phosphate (mmol/l)</th>
<th>Inorganic Phosphate (mmol/l)</th>
<th>Serum Calcium (mmol/l)</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>145.93196.5</td>
<td>3.62+1.3</td>
<td>1.58+0.36</td>
<td>29.7V7+11.4</td>
</tr>
<tr>
<td>11 ~ 20</td>
<td>155.0+89.5</td>
<td>2.08+0.55</td>
<td>1.6+0.2?</td>
<td>28.2+10.12</td>
</tr>
<tr>
<td>21 ~ 50</td>
<td>126.5+18.5</td>
<td>2.25+0.56</td>
<td>1.76+0.085</td>
<td>35.5+17.5</td>
</tr>
<tr>
<td>31 ~ i0</td>
<td>140.5+16.5</td>
<td>1.62+0.14</td>
<td>1.73+0.32</td>
<td>23.5+0.5</td>
</tr>
</tbody>
</table>

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, inorganic phosphate with the fall of glomerular filtration rate.

There was significant statistical correlation between creatinine clearance and alkaline phosphatase ($P = <<.012$), 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. $\bar{x} = 25$ 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 groups.

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 ($P = ^{>}.001$).
Fig. 1 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 ($P = \ldots$).

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 ($P = 0.012$).

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 ($p = \ldots$).
FIG. 1  AGE DISTRIBUTION
FIG. 3 EFFECT OF DURATION ON SERUM ALKALINE PHOSPHATASE

P = < 0.001

DURATION (MONTHS)
MEANS OF ALKALINE PHOSPHATASE AND CREATININE CLEARANCE

![Graph showing means of alkaline phosphatase and creatinine clearance.]

P < .01
FIG. 5 MEANS OF INORGANIC PHOSPHATE AND CREATININE CLEARANCE
FIG. 6 MEANS OF SERUM CALCIUM WITH CREATININE CLEARANCE

P < .04
Renal osteodystrophy as first described by Clement Lucas in 1883 (1) and later reported by Fletcher in 1911 (5) is a bone 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 proximal muscle 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) causes symptoms is very variable i.e. in Oxford renal Unit only 10-20% 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 osteodystrophy. 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 $10_{29}^{0}$ mls/min which is much better than other studies (26) in which patients had poorer renal functions and must be maintained on dialysis tending to have severe forms of renal osteodystrophy. 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 restriction 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). *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 these 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 starts is difficult to determine because some patients have been living fairly normally with impaired renal 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 straight 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 duration of illness and biochemical renal osteodystrophy (rise in alkaline phosphatase 100 + 85. ^ mmol/1 normal range 30 - 11.5 mmol/l).

In this study most of the patients were not on regular dialysis and therefore did not 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 ± 13.9 months.

It has been reported elsewhere by certain authors that females are more liable to skeletal disease (23) in end stage renal failure. The reason for 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 17.7 mmol/l was found in patients with clinical renal osteodystrophy. There was no statistical correlation between clinical presentation and acidosis (P > .50). There is no evidence to indicate whether or not systemic acidosis interferes with initiation of mineralization in the osteid bone or not (15). This is because correction of the acidosis does not influence renal osteodystrophy and yet appropriate treatment with vitamin D will cure azotaemic rickets and osteomalacia even when acidosis is left untreated. Cochran and Nordin (24) have however shown that acidosis does affect bone mineralization firstly because of its hypocalcaemic effect and secondly through its metabolic "hypophosphataemia" which occurs 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, (1B)
secondary hyperparathyroidism develops and as in this study the mean inorganic phosphate was $3.3\pm 1.25$ mmol per litre (normal range 0.81 - 1.36 mmol/l) showing marked significant statistical correlation ($\cdot 25^{\cdot} - P < 5$) with clinical renal osteodystrophy. Hyperphosphataemia does also inhibit $1,25 (\text{OH})_2$ production (14) leading to impaired intestinal calcium absorption and subsequent hypocalcaemia. In this study the mean serum calcium was $1.46 \pm 0.27$ mmol/l (normal values 2.25 - 2.50 mmol/l) showing significant statistical correlation ($P < 0.01$) with clinical renal osteodystrophy. Apart from hypocalcaemia contributing to PTH hypersecretion, there is also impaired renal degradation leading to its elevated levels in chronic renal failure. Even though it was not possible to estimate immunoreactive PTH in these patients it can be assumed that with such markedly raised inorganic phosphate, low calcium and very 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.
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 and tensile strength.

Collagen molecule is a polymer of tripeptides. Hydroxyproline constitutes 10% of the amino acid residues in collagen. It is derived within the osteoblast by hydroxylation of amino acid, proline, during collagen biosynthesis. It is released into circulation as hydroxyproline during bone collagen degradation. It is not reutilized and therefore either degraded in the liver or excreted normally in the urine (52). The cellular phase is essential for day to day formation, remodeling and bone resorption, the process which condition and maintain skeletal integrity. 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
alkaline phosphatase tend to 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 bone histology, elevated alkaline phosphatase may be the first indication of renal 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 (31) 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 (raised alkaline phosphatase) renal osteodystrophy (P<0.001). Isoenzymes were not studied but it is certain that raised alkaline phosphatase was from bone and not liver because these patients had no gastrointestinal problems and also where such study has been performed (3) it was 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 done 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 60 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 50 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 our patients.

Taking creatinine clearance as a determinant of deteriorating renal function, it was found that with the falling glomerular filtration rate, there is rise in incidence of 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 been reported by other authors. In the management of azotaemic renal disease, lowering of serum inorganic phosphate is of vital importance.

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

Serum alkaline phosphatase is an important indicator of renal osteodystrophy. It has been used and confirmed histologically by certain authors elsewhere. In centres where biochemical estimation of serum or urinary hydroxyproline and or immunoactive parathyroid hormone (iPTH) 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:) were 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 haemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD) is started.
1. Liu, S.II. and Chu, H.I. (1913) Studies calcium and phosphorus metabolism with special reference to pathogenesis and effects of dehydratachysterol and iron« Medicine, Baltimore 23; 103 (23^)


Fletcher II.M. (1911)
Proc. R. Soc. Med. k\ 95

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


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*


13» Strieker G et ale, Micropuncture study of inorganic phosphate excretion in the rat.


15o Stanbury, S.W. Done Disease in uraemia
Am. J. of Med. kk: 71k - 72k (1968)

17. Curbun J. w, Loppel M«H» Drichraan A.S. et alt


18. Eyanson J.M. (i960) The response to the infusion of parathyroid extract in hypocalcaemia state; Clin. Eci. 31:

19. Litzow, J.Rf Lentann, J. and Lennon, C.J.

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).


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


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

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


32. Avioli, L.V,, Sharp; C. and Birge, S.J.,


3'1o Kanis J.A.; Cundy „T.; Earnshaw M. et al