Spectrum of renal bone diseases in Sudanese children with chronic renal failure


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Abstract

Background
Disturbance in mineral and bone metabolism are common in children with chronic kidney disease (CKD). A large body of evidence indicates that renal osteodystrophy (ROC) affects skeletal growth and development and may result in increased morbidity and mortality.

The purpose of this study is to determine the prevalence and types of ROC and to study the clinical and radiological manifestations of ROC.

Patients and Methods
This is a cross-sectional survey of children with chronic renal failure in 5 main dialysis centers in Khartoum state. A designed questionnaire was conducted for data collection including personal details, social and dietary history, dialysis history and prescriptions, growth parameters, diagnosis, clinical picture, investigations and management.

Results
The study included 57 children with chronic renal failure (CRF) of whom the majority (75.4%) reached end stage renal failure (ESRD). The cause of renal failure was undetermined in 28 patients (49.1%). The mean duration on dialysis was 14 months. The majority of children (n=22) (44.8%) had moderate growth impairment. Renal osteodystrophy was documented in 36 patients (63.9%). The most common clinical presentation of ROC were bone pain, joint pain and pruritis, they accounted for 58.8%, 52.9% and 52.9% respectively. The most common radiological findings were osteopenia (88.8%), subperiosteal bone resorption (72.2%) and delayed bone age (69.4%). The predominant pattern of ROC was secondary hyperparathyroidism (2ry HPTH) (52.6%).

Conclusion
Renal osteodystrophy is a common complication in Sudanese children with CRF with the predominance of secondary hyperparathyroidism. The management of children with CRF should be in a paediatric nephrology unit through a multidisciplinary team approach and the treatment should be individualized.

Key words: Renal osteodystrophy, Secondary hyperparathyroidism, Chronic Renal Failure, Haemodialysis

Introduction
Renal osteodystrophy is the disorder of mineral metabolism that affects the skeleton in patients with CRF. It may result in considerable morbidity in children; it affects skeletal growth and development leading to bone deformities and often deceleration of
linear growth\(^1\). Children with ROD are usually asymptomatic; symptomatic children tend to have significant biochemical and radiological abnormalities. The spectrum of skeletal abnormalities seen in ROD is classified according to the state of bone turnover; high turn over represents hyperparathyroidism, low turn over represents osteomalacia, adynamic bone disease and mixed ROD\(^2\). The prevalence of ROD among patients with CRF and those on maintenance dialysis is 60 - 90\(^{\circ}\)\(^3,4,5\). Secondary hyperparathyroidism was the most prevalent lesion in Europe in the early days of chronic dialysis (80\%) and remains so in developing countries\(^6\). However, low turnover bone lesion without aluminum toxicity has been increasing in the paediatric population\(^6\). The improved medical and surgical management have led to prolonged and better quality of lives of children with CRF, and changed the specific pattern of ROD. Bone biopsy remains the gold standard test in the assessment of ROD but due to its invasive nature it is not performed routinely in clinical practice\(^2\). Parathyroid hormone (PTH) acts on the kidney and bone via activation of the adenylate cyclase. Most changes in PTH occur with changes in serum calcium and hence it is considered a useful test in detecting high and low turnover bone disease\(^7\).

The aim of this study was to determine the pattern and magnitude of ROD in Sudanese children and to study the clinical and radiological manifestations of ROD.

**Material and Methods**

This is a cross sectional survey of children with chronic renal failure in 5 main dialysis centers in Khartoum state (Dr. Salma Dialysis & Kidney Transplantation Centre, Dialysis Unit – Soba University Hospital, Dialysis Unit – Khartoum Teaching Hospital, Bahri Renal Centre, and Dialysis unit - Ahmed Gasim Hospital). The dialysis centers are adult dialysis units apart from Soba University Hospital which is a paediatric dialysis unit which later became the main paediatric nephrology centre.

The data was collected over a period of four months from November 2003 to March 2004 by the first author. A total of 57 children aged 3 months to 18 years were included. Chronic renal failure was defined as a glomerular filtration rate (GFR) of less than 50 mls/min/1.73 m\(^2\) body surface area for at least 3 months determined by Schwartz formula: GFR (ml/min/1.73m\(^2\)) = K (constant) X ht (cm) / creatinine (mg/dl). (K = 0.33 for pre-term infants, 0.45 term infants and up-to one year, 0.55 children and adolescents to 13 years and 0.65 in adolescent males\(^8\).

Treatment modalities included supportive medical treatment, intermittent peritoneal dialysis and haemodialysis.

A questionnaire designed for data collection included personal details, social and dietary history, dialysis history and prescription, growth parameters, diagnosis, clinical picture, investigation, and management.

Children’s growth was determined using the international standards for weight and height (NCHS-Standards) specific reference standards as recommended by WHO\(^9\). Indices for height for age and weight for age were constructed and Z-Scores were calculated using the cut off points as follows: normal when Z-Score is more than -1 SD, moderate when Z-Scores is less than -2.99 SD and severe when the Z-Scores is less than -3 SD.

A blood sample for determination of biochemical parameters (alkaline phosphatase, total calcium and phosphate) was taken before dialysis session. Automated machine (Autoanalyzer) has been used to measure serum calcium, serum phosphate and alkaline phosphatase using 0.5 ml serum, normal reference values were
8.1-11.5 mg/dl, 3.5-5.0 mg/dl and 90-280 ul/l respectively. Radioimmunoassay was used to measure the serum PTH, depending on the serum PTH levels, children were divided into three groups:
1- Hyperparathyroid bone disease (PTH >450 pg/ml).
2- Adynamic bone disease (PTH < 60 pg/ml).
3- A group with apparently normal PTH (PTH 60 to 450 pg/ml), they may show symptoms, signs and/or radiological bone changes (10).
Bone X-rays were taken from wrist, spine and pelvis and were interpreted by a consultant radiologist.
Consent was taken from the patients and/or parents for all children. After diagnosis the plan of management has been discussed with each unit.

Statistics
Data were entered into statistics software SPSS 10 for analysis. It was represented as means +/- SD. Comparison of the means was performed using an independent sample T-test and Spearman rank order correlation was used to assess the inter-relationship between various examined markers. P. value less than 0.05 was considered significant.

Results
The study included 57 children with a mean age of 12.5 years (Range: 3 months – 18 yrs), male patients were 34 (59.6%). Fourteen patients (24.6%) were diagnosed as CRF and 43 (75.4%) were end stage renal failure (ESRD). The cause of renal failure was undetermined in 28 (49.1%) patients (Table1).

<table>
<thead>
<tr>
<th>Cause</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>28</td>
<td>49.1</td>
</tr>
<tr>
<td>Chronic GN</td>
<td>9</td>
<td>15.8</td>
</tr>
<tr>
<td>Obstructive Uropathy</td>
<td>9</td>
<td>15.8</td>
</tr>
<tr>
<td>Stone</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>RPGN</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Barters Syndrome</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Alport Syndrome</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>100%</td>
</tr>
</tbody>
</table>

The majority of patients 34 (59.6%) were on haemodialysis, 13(23%) were on intermittent peritoneal dialysis and 10(18%) were on conservative management. The mean duration on dialysis was 14 months while the mean duration on conservative treatment was 24 months. Renal osteodystrophy was documented in 36 (63.1%) patients. The mean height for age and weight for age Z-Scores distribution for patients with CRF was -2.1 standard deviation (SD) and the majority 22 (44.8%) of children had moderate growth impairment. The most common clinical findings of ROD were bone pain, joint pain and pruritis, they accounted for 20 (58.8%), 18 (52.9%) and 18 (52.9%) respectively (Table 2).

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>20</td>
<td>58.8</td>
</tr>
<tr>
<td>Joint pain</td>
<td>18</td>
<td>52.9</td>
</tr>
<tr>
<td>Pruritis</td>
<td>18</td>
<td>52.9</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>15</td>
<td>44.1</td>
</tr>
<tr>
<td>Deformities</td>
<td>12</td>
<td>35.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>11.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Fractures</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Tissue of calcification</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>
Most patients with ROD had high serum phosphorus $\text{PO}_4$, 23 (63.8%), high PTH level, 27 (75%) and high alkaline phosphatase level, 30 (83.4%). The most common radiological findings were osteopenia, subperiosteal bone resorption and delayed bone age, they accounted for 88.8%, 72.2% and 69.4% respectively (Table 3). The majority of children 44 (77.2%) were not compliant with their diet although one alpha and calcium carbonate were given to almost all children 52 (91.2%) and 53 (93%) respectively. The dose was adjusted for weight or surface area for only two children receiving one alpha and in only one child receiving calcium carbonate. The predominant pattern of ROD was secondary hyperparathyroidism (2ry HPTH) 30 (52.6%), Adynamic bone disease was seen in 3 (5.2%) and the remaining children had apparently normal PTH (PTH 60 to 450 pg/ml) but they showed symptoms, signs and/or radiological bone changes 21 (36.8%).

Table (3): Radiological findings of patients with renal osteodystrophy

<table>
<thead>
<tr>
<th>Radiology</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia</td>
<td>32</td>
<td>88.8</td>
</tr>
<tr>
<td>Bone resorption</td>
<td>26</td>
<td>72.2</td>
</tr>
<tr>
<td>Delayed bone age</td>
<td>25</td>
<td>69.4</td>
</tr>
<tr>
<td>Brown tumour</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Loozer zone</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Rickets like</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Finger tufting</td>
<td>2</td>
<td>5.5</td>
</tr>
<tr>
<td>Osteosclerosis</td>
<td>2</td>
<td>5.5</td>
</tr>
<tr>
<td>Slipped femoral epiphysis</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Fractures</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td>Striations</td>
<td>1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

**Discussion**

Bone metabolic disorders have always been of the most important complications associated with chronic renal failure. Renal osteodystrophy is generally noted when the kidney loses about 50% of its function and almost all patients are affected when dialysis is required\(^7\). In our study the prevalence of renal osteodystrophy was 36 (63.1%). A comparable prevalence has been reported\(^3\) and a higher prevalence was also reported from the UK and Japan after bone biopsy. As in many studies the development of ROD was seen more in children on dialysis 32 (88.8%) while only 4 (11.2%) in the pre-dialysis group had ROD\(^3,4,11\). However, more children in this group could have been detected if bone biopsy was done. The specific patterns of ROD vary considerably between countries and may change during selected therapeutic interventions. Our data showed that secondary hyperparathyroidism was the predominant pattern of ROD seen in 52.9%, this was also shown in other studies\(^6,11,12\). The majority of children with ESRD were on haemodialysis (59.6%). The dialysis was inadequate and performed twice per week in adult centres and only one paediatric centre was performing dialysis thrice per week. Intermittent peritoneal dialysis (IPD) using a hard catheter was used in 23% of children, continuous ambulatory peritoneal dialysis
CAPD and automated peritoneal dialysis APD was only introduced recently. This regimen of inadequate dialysis was shown to have a detrimental effect on the child’s wellbeing, growth and the development of ROD\(^\text{\footnote{13}}\).

ROD in children presents with non-specific symptoms and signs and is often unnoticed. The most common clinical findings of the study group were bone pain, joint pains and pruritis, they accounted for 58.8%, 52.9% and 52.9% respectively; similar common clinical manifestation has also been reported\(^\text{\footnote{14}}\). This could be due to inadequate dialysis, high phosphate levels and increased PTH.

A substantial proportion of children have growth impairment (height for age 65.3% and weight for age 75.5%), the mean height for age and weight for age was -2.1 SDS. These results were also seen in other studies\(^\text{\footnote{15}}\). It is well known that ROD causes growth retardation and skeletal deformities\(^\text{\footnote{6}}\).

The radiographic features of ROD vary considerably between different countries; this difference reflects variation in the type of skeletal diseases observed\(^\text{\footnote{13}}\). In a study from Turkey osteopenia was seen in almost all patients, while rickets, osteosclerosis, and pseudo-fractures were seen in 47.6%, 14.2% and 4.7% respectively\(^\text{\footnote{16}}\). In our study osteopenia was seen in 88.8%, other lesions were bone resorption 72.2%, tufting of fingers 5.5% and brown tumors 2.7%. There was a significant correlation between the rise of PTH and bone resorption (P.value <0.05). This was shown also in other studies\(^\text{\footnote{6,16}}\). There was a statistically significant difference between bone age and chronological age. Delayed bone age was seen in 49.1%, the mean bone age was 10.7 years compared to 12.5 years chronological age.

The optimal treatment of ROD in children, prevention and therapeutic strategies must be achieved early in order to minimize the complications of the growing skeleton. In our study 77.2% were non-adherent to their diet and the majority were non compliant with their medications.

In conclusion ROD is a common complication in Sudanese children with CRF with the predominance of secondary hyperparathyroidism. The management of children with CRF should be in a paediatric nephrology unit through a multidisciplinary team approach and the treatment should be individualized.

References

أنواع مرض حثل العظام وسط الأطفال السودانيين المصابيين بالفشل الكلوي
محمد عبد الرحيم
زين كرار
الجناحي علي
ملخص البحث:
 يعتبر مرض حثل العظام المصاحب لمريضي الفشل الكلوي من الأمراض التي تؤثر على الهيكل العظمي للجسم. وهو من المصادر الثلاثة الهامة والخطيرة
اراء اليم نامما ما قد يؤديه للاطفال اجريت هذه الدراسة على 57 مريض بالفشل الكلوي في الفترتين من 2001 إلى 2003 في مركزائن بالكنيكي: مركز الدكتور سامي شيركي، ودريس الكلية، وحيدة غسيل الكلية، وحدة غسيل الكلية، كل من مستشفى سوها الجامعي، مستشفى الخرطوم التعليمي، مستشفى أحمد حسن، كل من مركز بحري
لاعصاب ور компании
الهدف من الدراسة هو تحديد النتائج الأكثر شيوعا من مرض حثل العظام عند الأطفال والأعراض المصاحبة وكذلك العلاج
تغطيت الدراسة 49.1% من الأطفال، وتشمل نسب رفع في العظام عن طريق الكلي في 64.1% من الطفل، وتشمل نسب رفع في العظام عن طريق الكلي في 44.8% من الأطفال
كانت نسبة الأطفال المصابين بفصول في للطحية الكلية 14.6% بينما كانت نسبة الأطفال المصابين بالفشل الكلوي 14.1% بنسه 49.6% منهم وهم بوضع الانصيال الدموي
كانت نسبة حثل العظام 81.5% وتشمل نسبة 10% من الدراسة، وتشمل نسبة الفشل الكلوي 25.4% للكليه في النصف مولات الدم في 44.8% من الأطفال
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وقد اتفق الكلي بالعصب على العظام ك أن أكثر اعراض مرض حثل العظام شيوعا في الأطفل 88.8% في الكلية، وتشمل نسبة الفشل الكلوي 25.4% للكليه في النصف مولات الدم في 44.8% من الأطفال
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 وهب او تجاوزها. 75.2% وذلك نادر الكلي، وتشمل نسبة الفشل الكلوي 25.4% للكليه في النصف مولات الدم
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