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Bone disorders in pediatric patients with end-stage of kidney failure

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Abstract

The children with stage5 chronic kidney disease is increasing, and they are experiencing various complications, with renal osteodystrophy (secondary hyperparathyroidism) being the most significant. **Objective**: To identify the incidence of renal osteodystrophy in end –stage kidney failure pediatric patients on maintains Hemodialysis visiting at pediatric dialysis units, Tripoli University Hospital, Tripoli, Libya. **Methodology:** 23 pediatric patients followed up at the hospital with diagnosis of Chronic Kidney Disease (CKD) stage 5 on hemodialysis of the age between 1 to 18 years (11 girls and 12 boys) were involved in the study. Multiple biochemical markers of renal osteodystrophy were included (serum calcium, phosphorus, Parathyroid Hormone (PTH), Alkaline Phosphatase (ALP), Vitamin D), which is collected from medical files of patients. All pediatric patients were assessed by using biochemical marker, clinical feature and X-ray some of them, to diagnosis the presence of mineral bone diseases. **Results**: The mean and standard deviation of age were 11.43±3.95 years. 11(47.8%) were girls and 12(52.2%) were boys. Secondary hyperparathyroidism (renal osteodystrophy) was found in 69.6% with mean values of PTH of children was 725.57±644.11. Also the mean Ca level was 8.44±0.95. High percentage of bone pain and itch presented was78.3% and 65.2% of patients, respectively, which they related to hyperparathyroidism. X-ray was conducted on

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selected patients to facilitate the assessment of bone diseases in children with chronic kidney diseases.

In Conclusion, biochemical analysis, clinical signs and X-ray provided relatively accurate information for diagnosis and treatment. The clinical characteristic of this disease indicate that early detection could be the most effective approach to change its progression.

Keywords. Osteodystrophy; hyperparathyroidism; haemodialysis; bone disease; pediatric ESKD.

اضطرابات العظام لدى الأطفال المصابين بالفشل الكلوي في المرحلة النهائية

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1- قسم المختبرات الطبية – كلية العلوم و التقنيات الطبية – طرابلس – ليبيا

2- استشاري أمراض الكلى للأطفال – مستشفى جامعة طرابلس – طرابلس – ليبيا

3- أستاذ أمراض الدم والنسيج

الملخص

عدد الأطفال الذين يعانون من أمراض الكلى في المراحل النهائية في تزايد، وهم يعانون من مضاعفات مختلفة، وأبرزها الحثل العظمي الكلوي (فرط نشاط الغدة الجار درقية الثانوي) .

الأهدف: تحديد معدل انتشار الحثل العظمي الكلوي لدى مرضى الأطفال الذين يعانون من الفشل الكلوي في مراحله النهائية والذين يخضعون لغسيل الكلى في وحدات غسيل الكلى للأطفال بالمستشفى الجامعي طرابلس\ طرابلس- ليبيا.

المنهجية: تمت متابعة 23 مريضا من الأطفال الذين تتراوح أعمارهم بين 2 و17 عاما (11 طفلة و12 طفل) في المستشفى مع تشخيص مرض الكلى المزمن في المرحلة الخامسة والخضوع لغسيل الكلى الدموي. تم تضمين معايير كيميائية حيوية مختلفة للحثل العظمي الكلوي في الدراسة مثل: الكالسيوم في الدم، الفوسفور، هرمون الغدة الجار درقية، فيتامين د وانزيم (الفوسفات القلوي)، وتم جمعها من الملفات الطبية للمرضى. تم تقييم جميع المرضى باستخدام التحاليل الكيميائية الحيوية والأعراض السريرية وصور أشعة لبعض منهم لتشخيص وجود أمراض العظام المعدنية.

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النتائج: كان متوسط العمر والانحراف المعياري 11.43±3.95 سنة. 11(47.8%) من المرضى كانوا إناثًا. 12 (52.2%) كانوا من الذكور. تم العثور على فرط نشاط الغدة الجار درقية الثانوي (الحثل العظمي الكلوي) بنسبة 69.6 % مع متوسط مستويات هرمون الغدة الجار درقية للأطفال.644.11± 725.57. كانت نسبة الألم العظمي والحكة لدى المرضى مرتفعة، حيث بلغت 78.3% و 65.2% على التوالي، وارتبطت بفرط نشاط الغدة الجار درقية. تم إجراء صور أشعة لعدد من المرضى لتسهيل تقييم أمراض العظام لدى الأطفال الذين يعانون من أمراض الكلى المزمنة.

الاستنتاج: قدمت التحاليل الكيميائية الحيوية والأعراض السريرية وصور الأشعة معلومات دقيقة نسبيًا لتشخيص وعلاج هذه الحالات. تشير الخصائص السريرية لهذا المرض إلى أن الكشف المبكر قد يكون النهج الأكثر فعالية لتغيير مسار تطور المرض.

الكلمات المفتاحية: خلل النسيج العظمي، فرط نشاط الغدة جار الدرقية، غسيل الكلى، أمراض العظام، الفشل الكلوي النهائي عند الأطفال.

Introduction

Chronic kidney disease CKD represents a significant public health concern, impacting approximately 8-18 % of the global population [Stern, 2021]. The kidneys have a critical role in the management of calcium, phosphate, parathyroid hormone, and vitamin D metabolism. [Lavinia, 2023، Avioli, 1978]. Chronic kidney disease is a change in structural and functional of kidney due to multiple causes. It is commonly defined as a reduction in kidney function, measured by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2, persisting for at least 3 months [Kamyar ,2021; Webster ,2017]. Structural abnormalities, such as (e.g. renal hypoplasia or posterior urethral valves) are more prevalent between pediatric patients [Francesca, 2016: Warady 2007]. Markers and symptoms of CKD result from progressive uremia, anemia, and volume overload, electrolyte disturbances, mineral and bone disorders, and certainly lead to death if left untreated. Renal replacement therapy, either in the form of chronic dialysis or kidney transplantation, but dialysis still the prevailing treatment option for most patients with kidney failure. [Kamyar,2021; Song ,2016]. The proportion of patients on Haemodialysis compared with peritoneal dialysis elevates with age.

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Haemodialysis is usually carried out in a center three times a week for 3–5 h per session. [Lesley, 2017; Ma A ,2013]. The effect of CKD on pediatric patients, causing various unfavorable outcomes, included: fractures, pain, bone deformities, difficult to walk and growth failure that influence the quality of life of these children and adolescents, and it continues with them until puberty [Emilia, 2020; Wesseling, 2015]. Children with stage 5 of chronic kidney disease and on hemodialysis showed substantial complexity, including growth retarding, anemia, extra skeletal calcification, cardiovascular disease and mineral bone disorders. (Keia R 2020). Chronic kidney disease-mineral bone disease (CKD-MBD) is defined as a systemic disturbance of mineral and bone metabolism caused by CKD, which is characterized by abnormalities in bone and mineral metabolism and/or extra- skeletal calcifications. [Ornatcha ,2022 ; Moe S ,2006] .The term Renal osteodystrophy (ROD) refers to alternation the bone morphology associated with chronic kidney disease (CKD) [Lavinia .2023: Lalayiannis ,2020] . The global distribution of ROD with end stage of renal failure (ESRF) and those regulated on hemodialysis is 90 to 100% [Javed .2017; Buargub .2006]. The secondary hyperparathyroidism is directly associated with the progression of CKD-MBD. Kidney failure causes hypocalcemia and hyperphosphatemia. This results from a decrease of 1-alpha-hydroxylation of 25-hydroxyvitamin D, which leads to a decline in intestinal absorption of calcium. The parathyroid gland stimulates to hypocalcemia and produces more PTH. Also, lowering glomerular filtration rate (GFR) produces phosphate retention, which stimulates the osteocytes to secrete Fibroblast growth factor 23 (FGF23). [Lavinia ,2023 ; Langman, 2005] . Blood calcium levels decrease not only because of calcitriol deficiency, but also due to phosphate (P) retention and the development of bone resistance to PTH action [Lavinia .2023; Santos. 2021]. Also persistent elevation of PTH level stimulates osteoblastic activity and induce bone turnover [Katherine, 2013; Leek, 1993]. In 2006, Kidney Disease :Improving Global Outcomes (KDIGO) guidelines were recommended based on parameters for classification of ROD is (turnover, mineralization, and volume), using the TMV system. [Emilia, 202: Moe S, 2006] . The diagnosis of renal osteodystrophy (ROD) is very important, and bone biopsy, which is the valuable standard diagnostic method, is necessary for

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an accurate diagnosis. [Emilia, 2020; Moe S, 2006]. However, this diagnostic method requires specialized trained personnel for its interpretation, which hinders its use in clinical practice [Javed , 2017 ; Buargub ,2006] . currently non-invasive methods of assessing bone health in pediatric patients are available, involving diagnostic imaging such as skeletal X-rays and ultrasonography of parathyroid gland [Awatef ,2022] and commonly used biochemical parameters such as parathyroid hormone(PTH), calcium (Ca), phosphate (P), alkaline phosphatase (ALP), and 25-hydroxyvitamin D [Sevcan ,2020 ;Lalayiannis ,2020]

The aims of the study:

1- This study was conducted to determine the incidence of mineral and bone disorders in pediatric with end stage chronic kidney disease on maintenance hemodialysis at pediatric dialysis unit at university hospital Tripoli.

2- To shed light on the, symptoms and biochemical parameters for children have renal osteodystrophy .

3- To explain the patterns of renal osteodystrophy by using x-ray of skeletal children's.

Material and Methods

A cross-sectional study was conducted at Pediatric Dialysis Unit in Tripoli University Hospital from December 2024 to January 2025 .Twenty-three patients were included through Purposive sampling. All patients have stage 5 of renal failure (ESRF) are on Haemodialysis (twice/thrice a week for >3 months).

Data collection procedure

All patients visited the Pediatric Dialysis Unit, Tripoli University Hospital ، Tripoli in Libya. This study included pediatric patients with chronic kidney failure stage 5 with an estimated GFR of <15 ml/min/1.73 m^2. The number of patients was 23, male and female, between the ages of 1years to 18 years with chronic kidney disease stages 5 and all of them in regular Haemodialysis in the dialysis unit. Some of data was taken by medical files of patients in the dialysis unit and some from the children's parents. Medical recorders were included; age, gender, primary CKD diagnosis, age at start of dialysis, and X-ray images of the bone was done in some of them. Serum biochemical analysis (Calcium, phosphorus, alkaline phosphatase, vitamin D, and PTH) .

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Statistical Analysis

Statistical analysis was conducted using the Statistical Program for Social Sciences (SPSS version 25.0). The first version of SPSS was released in 1968 after being developed by Norman H. Nie , Dale H.Bent and C. Hadlai Hull .[Gunarto ,2019]. The SPSS used for enter and analyze data. Descriptive statistics were used and all results are presented as means ± standard deviation, maximum and minimum value. Mean and standard deviation were calculated for quantitative variables such as serum calcium, vitamin D, phosphate, alkaline phosphatase and PTH. Frequency and percentage were computed for (Gender, Age, PTH, and ALP).

RESULTS

The study included 23 pediatric patients with CKD stage 5 and on regular hemodialysis. The age of the patients was less than 18 years.

Age and Gender Distribution

Out of 23 pediatric outpatients with chronic kidney disease (CKD) stage 5 on Haemodialysis، 47.8% (n = 11) of the study group were girls and 52.2% (n = 12) were boys, as shown in (Figure.1).

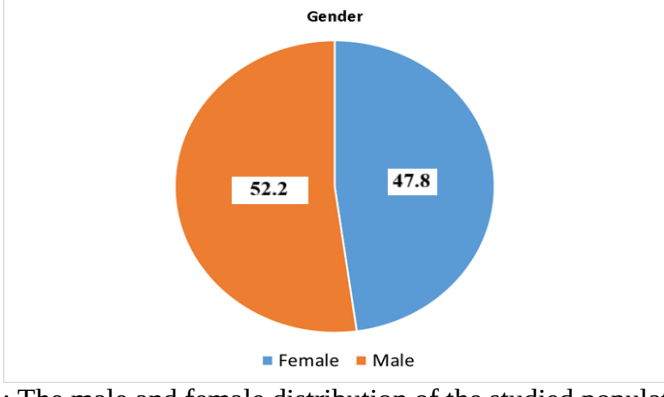

Figure 1: The male and female distribution of the studied population

The mean and standard deviation of age of all the studied group was 11.43±3.95 years, with a range in the present study from 1 to <18 years. Furthermore, the studied patients were classified in several groups based on age as 1- 6, 7-12 and 13-18 years. The age distribution in form of the percentage for all groups is shown in (Figure .2). The age groups of 1-6 years were 17.39 % ,7-12 years were 39.13 % and the 13-18 years was 43.48%.

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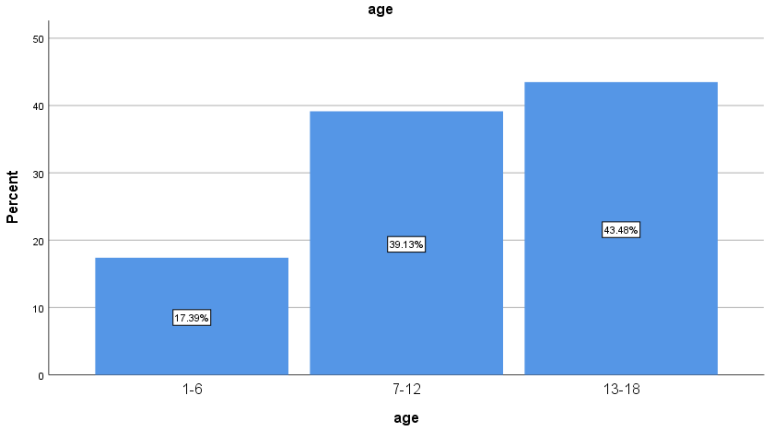

Figure 2: The age distribution of the studied population

The Biochemical Characteristic of the Studied Sample

Chronic kidney disease (CKD) is a condition characterized by a gradual loss of kidney function over time. The diagnosis of CKD depends on the measurement of laboratory and other variables. The laboratory diagnosis of CKD-MBD includes the use of laboratory testing of serum Parathyroid hormone (PTH), calcium, phosphorus, and alkaline phosphatases. (Table 3).

Table 3: The mean value of the Ca, P, ALP, PTH, Vitamin D and Ca x P levels of the pediatric patients with CKD stage 5 on hemodialysis

Variable	Mean ± SD	Minimum value	Maximum value
Ca (mg/dl)	8.44±0.95	6.90	10.26
P(mg/dl)	5.50±1.71	3.03	9.90
ALP(UI/L)	412.20±201.77	84	781
PTH (pg/ml)	725.57±644.11	69.41	2400
Vitamin D (ng/ml)	43.08±21.52	5.57	84.39
Ca x P	46.98±16.75	21.82	85.93

SD= standard Derivation & Ca = Calcium & P= Phosphor & ALP= Alkaline phosphatase & PTH= Parathyroid hormone.

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Among the studies patients in the present study, the maximum value of alkaline phosphatase was 781UI/L while the minimum was 84 UI/L, and the mean ± SD was 421.20 ±201.77 UI/L.

The normal level of alkaline phosphatase was detected only in 12 patients, while the other 10 patients have a high level according to the normal level for each age group reported in KDOQI, clinical practice guideline for bone metabolism disease in children with chronic kidney disease [KDOQI]. Furthermore, the average level of PTH of the entire sample was 725.57±644.11pg/ml, within the maximum value of 2400 pg/ml and minimum of 69.41 pg/ml.

(Figure 3) presents the distribution of PTH level among the number of patients. One of the 22 patients had PTH level below the target level, and 16 patients more than the target level (PTH target level, 100-300 pg/mL for stage 5 CKD), whereas six patients are in the range of the target level.

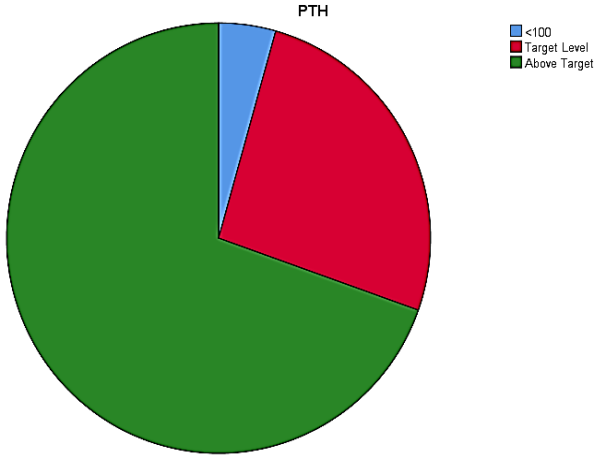

Figure 3: The PTH level distribution of the studied patients.

Symptoms Characteristic

Bone symptoms characteristic (bone pain, Bone fracture, Bone deformity and itch) related to hyperparathyroidism were also analyzed and the findings listed in (Table 4). The high percentages of bone pain and itch presented in 78.3% (n = 18). Furthermore, relative high percentage (47.8% (n = 11)) of the patients characterized by the presence of done deformity and 21.7% (n = 5) of the total patients are suffering from bone fracture as noticed in X-ray images.

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Table 4: Symptoms characteristic related to hyperparathyroidism.

No.	Variable	Percentage (%)
1	Bone pain	78.3%
2	Bone fracture	21.7%
3	Bone deformity	47.8%
4	Itch	65.2%

In this study, increased bone resorption was observed in a some of children with CKD-MBD through symptoms, X-ray performed on them and accompanied by an increase in parathyroid hormones above the target level which was 69.6% and alkaline phosphatase was 47.8% shown in tables (5,6).

There is no vital indicator to evaluate renal osteodystrophy. All currently available indicators have limited sensitivity in predicting bone complications like alterations in bone (mineralization and turnover) and vessels (vascular calcifications). Some serological criteria have been proposed for assessing ROD in children. [Sevcan et al 2020 : Haffiner et al 2013].

Table .5: Percent of parathyroid hormone in patients with CKD stage 5.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<100	1	4.3	4.3	4.3
	Target Level	6	26.1	26.1	30.4
	Above Target	16	69.6	69.6	100.0
	Total	23	100.0	100.0	

Table .6: Percent of alkaline phosphatase in patients with CKD stage 5.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Low ALP	1	4.3	5.3	5.3
	normal ALP	7	30.4	36.8	42.1
	High ALP	11	47.8	57.9	100.0
	Total	19	82.6	100.0	
Missing	System	4	17.4		
Total		23	100.0		

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Radiological Finding

The impact of elevated parathyroid hormone levels, phosphorus, and the decrease in calcium levels in patients with end-stage chronic kidney disease leads to disturbance in mineral and bone metabolism, CKD-MBD.

Renal osteodystrophy varies based on the data, manifesting as conditions such as (Osteitis Fibrosa Cystica, Adynamic bone disease, Osteomalacia, osteoporosis and calcinosis) which are characterized by several symptoms, including difficulty walking, bone weakness, bone deformity and an increased risk of fractures. Children in growing age may develop deformity in the lower legs in the form of bending inside or outside.

A hand photograph and AP plan anterior-posterior wrist X-ray image of the right hand of 14 years female patient with CKD stage 5 on Haemodialysis is shown in (Figure 4). It is very clear that the radiologic findings correspond to the clinical findings. The X-ray shows the changes is clearly in medial angulation radius and ulna at the articulation of the wrist joint.

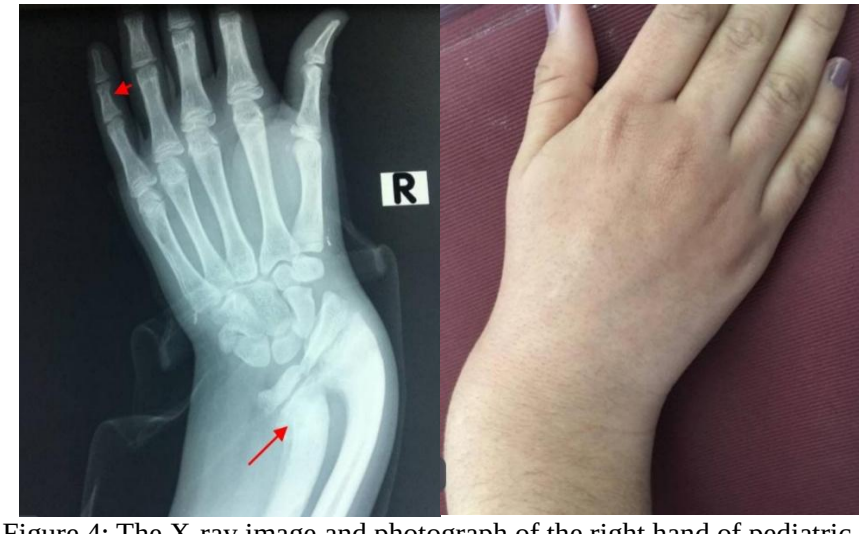

Figure 4: The X-ray image and photograph of the right hand of pediatric patient with CKD stage 5.

Bone resorption is the most frequent alteration of CKD which occurs in several locations. Calcinosis of chronic renal failure is cause of soft tissue calcifications in hemodialysis patients with chronic renal failure. The findings that can be seen in secondary

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hyperparathyroidism include soft-tissue and vascular calcification. (Figure 5) shows the X-ray image of anterior-posterior hand and wrist of male pediatric patient (17 years) with CKD stage 5. The X-ray image showed subchondral resorption at several interphalangs and metaphalangs. The vascular classification can be seen at medial side of the radius.

Anterior-posterior arm X-ray of female (15 years) with CKD stage 5 also showed soft calcification medial to the radius due to Henoch Schonlein Purpura on hemodialysis (Figure 6).

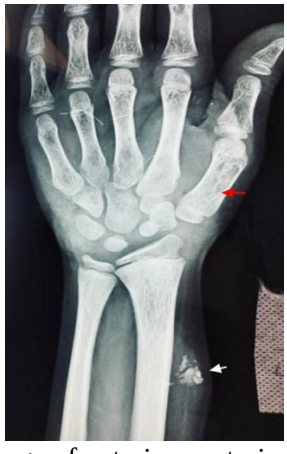

Figure 5: The X-ray image of anterior-posterior hand and wrist of male pediatric patient (17 years) with CKD stage 5.

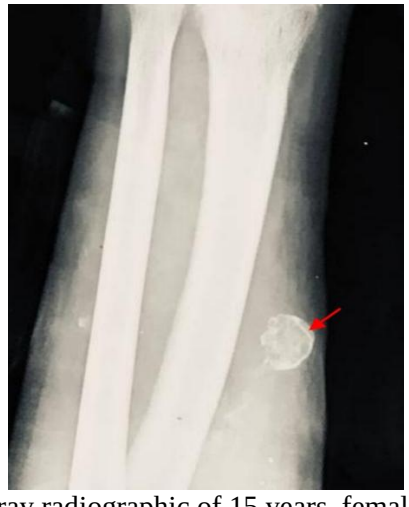

Figure 6: The X-ray radiographic of 15 years, female hand with CKD stage 5.

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Plain X-ray radiograph of hand for a young female patient (17 years) with CRF is shown in (Figure 7). The radiographic features show signs of secondary hyperparathyroidism. Radial aspects of the middle phalanx are affected because of subperiosteal erosion in hyperparathyroidism and is called aerosteolysis.

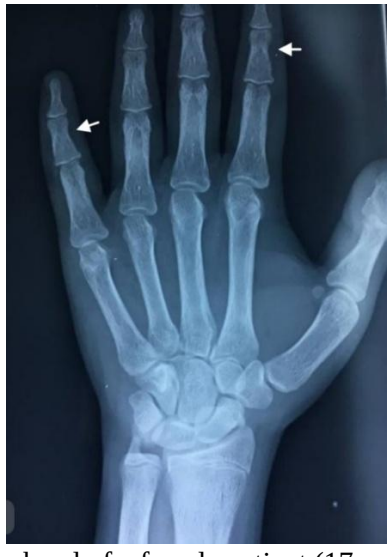

Figure 7: Plain X-ray hand of a female patient (17 years) with CRF.

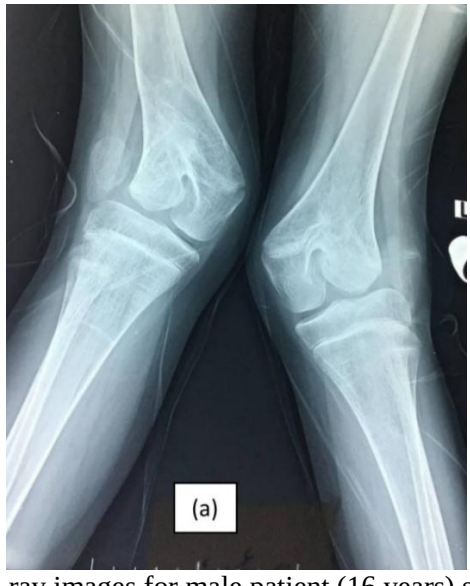

Figure 8: The X–ray images for male patient (16 years) stage 5CKD.

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(Figure 8) presents X–ray images for a pediatric patient (male, 16 years) with CRI was due to a posterior urethral valve. Showed an anterior-posterior knee joint X-ray with knock knee deformity.

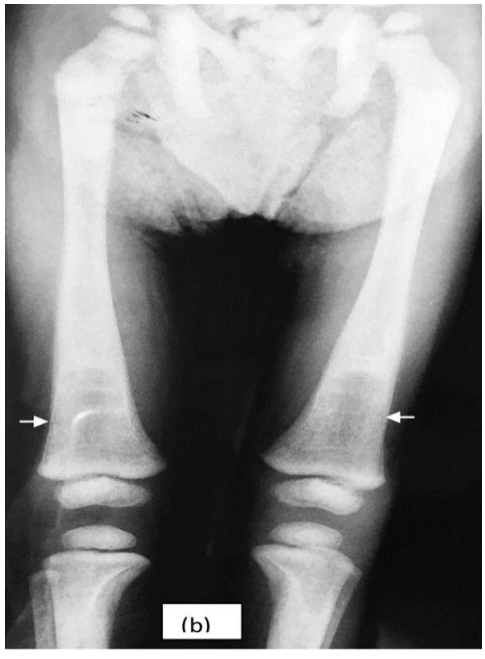

Figure 9: The X-ray radiographic of young male patient (3 years) with CKD stage 5 due to oxilosis on hemodialysis.

(Figure 9) shows the X-ray radiograph of a young male patient (3 years) with CKD stage 5 due to oxalosis on hemodialysis. Appearance the diffuse homogeneous nephrocalcinosis (oxilosis) change with normal bilateral kidney size. There was also increase in the density of pelvic bone sclerotic change.

DISCUSSION

Renal osteodystrophy is not absolutely cured, as a result, active control, regular and periodic monitoring becomes the only effective means of management [Haitao, Xiaoming, et al,2024]. Disturbance in mineral and bone metabolism are common in chronic kidney disease and significant cause of morbidity, extra-skeletal calcification that have been associated with increased cardiovascular mortality [Moe S , Drueke T ,2006].

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In this study, which relied on laboratory analysis, clinical evaluation and X-rays, it agrees with Sherif , Youssef …et al study in Saudi Arabia 2016 and Javed, Pooran … et al study in Pakistan 2017 regarding the diagnostic method for renal osteodystrophy. However, diverged from certain previously mentioned studies, which utilized bone biopsy and Dual-energy X-ray Absorptiometry DXA scans for diagnosis. This discrepancy is attributed to the high cost associated with these procedures.

This study describes the prevalence of CKD-MBD pediatric patients with end-stage kidney Failure on maintenance hemodialysis. In the present study, the mean PTH level was significantly elevated (725.57±644.11 pg/ml), with 69.6% of children experiencing secondary hyperparathyroidism, this aligns with Sevcan's et al, California ...2010 findings, where their results were 57% of patients exhibited high bone turnover and had secondary hyperparathyroidism, while 48% had abnormal mineralization. Although the differences in the type of dialysis.

Furthermore, ALP levels were elevated in 47.5% of patients, reinforcing the association between these biochemical markers and bone abnormalities.

The bone deformity and bone fracture were very clear on children with CKD stage 5, where was it percent 47.8%, 21.7%, respectively, which does not agree with Sherif's …et al study in Saudi Arabia 2016, where patients had bone deformity was 26.2% with a mean PTH level of 62.2 pmol/L. and bone fracture was 4.9%, the PTH levels in the current study were markedly higher, attributed to differences in sample size or the measurement unit used.

While the current study primarily focused on high bone turnover due to secondary hyperparathyroidism and clinical evaluation, its findings of elevated PTH and ALP levels align with Emilia's observations, 2020 in Brazil, supporting the association between these markers and bone turnover abnormalities, which was 29% showing abnormal mineralization, by bone biopsy and DXA scan.

Osteitis Fibrosa Cystica (OFC) being the most common pattern of renal osteodystrophy by (32%) in Javed study in Pakistan, in the present study also identified secondary hyperparathyroidism (OFC) as the most prevalent form of renal osteodystrophy, affecting 69.6% of patients, this discrepancy is due to difference in the age group targeted in the Pakistan study, where the mean age was 45.85 ± 13.5

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years. Also, Pakistan had 89% of patients with renal osteodystrophy, this higher prevalence than other studies due to deteriorating socio-economic conditions and unlimited usage of phosphate binders. In contrast, children with CKD stage 5 in our study receive regular medication such as Renagel.

However, in this study, X-ray imaging was used instead of DXA to identify bone deformities, which is consistent with A. D Lalayiannis' in London recommendation 2020 to avoid routine DXA in children with CKD , where concluded that (DXA) was not clinically useful in children with CKD.

But, we do not agree with them on the percentage of bone pain, which was 58% of patient, as our percent was higher in bone pain 78.3%. and this is due to the smaller sample size compared to theirs.

All studies emphasize the significance of biochemical markers (PTH, ALP, calcium, phosphate) in assessing CKD-related bone disorders (ROD). But, in addition to the biomarkers, the methods used for accurate bone assessment have varied between bone biopsy and X-rays.

CONCLUSION

In the present study, it was concluded that the distribution of renal osteodystrophy in pediatric patients with end stage chronic kidney disease on maintenance Haemodialysis was significantly increased. Determine the relationships between the biochemical variables of the studied pediatric samples and bone disorders through X-ray images of the bone. A sample consisting of 23 pediatric patients follow up with CKD stage 5 on Haemodialysis of the age between 1-18 years are participated in the present study and the data were collected from the patient's files at Tripoli University Hospital, but the X-ray images of the hands and leg bones were obtained for some of them.

The most common pattern of renal osteodystrophy was Secondary hyperparathyroidism (Osteitis fibrosa Cystica) in 69.6% of pediatric in this study. Among the studied sample, 11 patients had bone deformity and 5 patients with history of bone fracture.

Our study relied on biochemical laboratory analysis of (PTH, ALP, Ca, P, vitamin D), symptoms and X-ray images, for diagnosis

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of ROD, which although is a well predicator of bone histology, but not as precise as bone biopsy.

RECOMMENDATIONS

1. Further studies with a larger sample size and broader inclusion of dialysis methods are recommended for renal osteodystrophy pediatric patients to ensure statistical significance between variables.
2. Early detection of chronic kidney disease CKD helps reduce complications by performing regular analysis, particularly monitoring parathyroid hormone levels.
3. Developing new treatments that directly target improving bone health.
4. Improving dialysis protocols and kidney transplant opportunities for children.
5. It is recommended to educate parents on the importance of adhering to prescribed medications, limiting foods high in PH. and incorporating more Ca –rich foods into the diet.

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