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RENAL OSTEODYSTROPHY AND ITS ORTHOPAEDIC IMPLICATIONS IN CHILDREN WITH END-STAGE RENAL DISEASE

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Abstract

Renal osteodystrophy (ROD) is a cardinal skeletal manifestation of chronic kidney disease–mineral and bone disorder (CKD–MBD), most prominently seen in children with end-stage renal disease (ESRD). In this study, we examined the orthopedic burden, biochemical disturbances, and therapeutic outcomes of ROD in pediatric ESRD patients. While as the management protocols continue to evolve, the histologic subtypes of ROD and their musculoskeletal consequences have been an under-explored area in clinical research. A prospective observational cohort study was conducted at Civil Hospital Karachi (CHK), Karachi, and a total of 60 children aged 2–18 years with ESRD on dialysis were included. The implemented standardized data collection comprised; clinical examination, anthropometry, radiographic imaging (skeletal survey and bone-features on pelvis X-ray), iliac crest biopsy specimens for bone histomorphometry, and in-depth assessments of biochemical parameters that included serum calcium, phosphate, iPTH (intact Parathyroid hormone), ALP (alkaline phosphatase; a well-documented proliferating biomarker in CKD-MBD), vitamin D metabolites, FGF. Our findings showed that 73.3% had bone pain, 28.3% presented with pathological fractures and 48.3% had skeletal deformities. Growth retardation was detected in 68.3% of patients, it had significant association with higher iPTH levels, lower serum calcium and vitamin D levels and longer duration on dialysis ($p < 0.05$). Hyperparathyroidism was diagnosed biochemically in 90%, vitamin D deficiency in 70%, and hypocalcemia was documented in 75%. Radiographic osteopenia and subperiosteal resorption were common and related to biochemical derangements. Variable biochemical and radiological responses were, possibly reflective of this variability among treatment modalities which comprised phosphate

binders, vitamin D analogs, dietary restriction, dialysis adequacy with the most significant improvement seen following parathyroidectomy. Our findings offer a complete image of CKD-MBD in pediatric ESRD and point to the potential benefit of integrated metabolic control for orthopedic complications

INTRODUCTION

Renal osteodystrophy (ROD) is the bone pathology of chronic kidney disease, constituting the skeletal component of the systemic disorder described as CKD–mineral and bone disorder (CKD–MBD), including abnormalities of calcium, phosphate, PTH, vitamin D metabolism and soft-tissue calcification. In pediatric CKD, and especially in children progressing to end-stage renal disease (ESRD), ROD is almost universal, perturbing bone turnover, mineralization, and volume as well as affecting linear growth and skeletal development (Aguilar *et al.*, 2023).

Hyperphosphatemia arises as a consequence of reduced phosphate excretion with advancing kidney dysfunction, while vitamin D hydroxylation goes down, leading to hypocalcemia. The result is hypo-mineralization of the bone matrix due to a secondary disturbance in bone mineral metabolism; this, in turn, exacerbates PTH secretion and FGF-23, both of which dysregulate bone formation through abnormal inhibition of signaling pathways and altered remodeling cycles. We can classify ROD histologically using the TMV framework, turnover, mineralization, and volume, thus differentiating osteitis fibrosa, adynamic bone disease (ABD), osteomalacia, mixed forms, and normal morphology (Koumakis *et al.*, 2021).

In pediatric ESRD populations, ROD has significant orthopedic implications. A number of cases-control and cohort studies (including the CKiD (CKD in Children initiative) have noted that fracture rates in children with CKD were 2 to 3 times higher than in age-appropriate controls, with the former cohort demonstrating approximately 395/10,000 person years fractures among males and females at risk for fracture, respectively; this rate being ~323 versus ~162 per 10 KPY observed among male and female control population (Zhang *et al.*, 2023). One study determined that approximately 16% of pediatric CKD patients had experienced a fracture before enrolment, while during a median follow-up period of 4 years, incident fractures were found in 12.5%, evidence of an increased tendency for fractures even before ESRD onset.

Skeletal deformities similar to those seen in renal rickets develop commonly: bowed long bones, genu valgum, and slipped epiphyses of femur, humerus, radius or ulna. Pain, gait abnormalities, functional limitations, and mobility restrictions result from these structural anomalies. Growth failure is likewise common, even half of children with CKD fail to attain their genetic target height and secondary hyperparathyroidism and high alkaline phosphatase (ALP) are poor prognostic factors. The International Pediatric Peritoneal Dialysis Network (IPPN) registry reported that among pediatric peritoneal dialysis patients approximately 15% had clinical or radiographic evidence of bone disease such as rickets, osteopenia, limb deformity and bone pain (Bakkaloglu *et al.*, 2021).

Bone mineralization defects are particularly noteworthy. Children with glomerular or hereditary ESRD exhibit less mineralization abnormalities for a similar biochemical profile as pediatric ESRD patients who have CAKUT. In this cohort, serum ALP was significantly increased while FGF-23 levels were decreased in a sequence favoring the possibility of a biomarker-mediated connection between CAKUT and disordered mineralization (Chen *et al.*, 2018).

Importantly, this defect was present after adjusting for confounding variables suggesting a potential intrinsic osteogenic dysregulation in the setting of hypoxia.

The risk for fractures is also higher in adult patients with ESRD, being hip fractures related to 44% of fragility fractures and followed by vertebral fractures (with 32%). While pediatric fracture patterns may be distinct, these fractures share the common pathophysiology of bone fragility and either impaired or over-use remodeling due to the period of rapid growth and epiphyseal activity. Operative fracture management in pediatric ESRD is a yet studied area with limited data, adult series show increased rates of non-union, infection and postoperative complications when bone quality is compromised (de Bruin *et al.*, 2020).

In pediatric ESRD, therapeutics are targeted to alleviate CKD–MBD and to maintain skeletal health. To control it early, binders (calcium-based or sevelamer) and calcitriol supplementation or non-hypercalcemic analogues like paricalcitol; and use of calcimimetics (cinacalcet), are used to adjust PTH, avoid over-suppression and prevent adynamic bone disease. In children, limited pediatric-specific data exist regarding long-term orthopedic outcomes following these therapies and whether biochemical markers equate to fewer deformities or fractures (Maranduca *et al.*, 2024). Overall, ROD in ESRD children is marked by universal derangement of bone health with increased risk for fractures, deformities, pain and stunted growth. Mineralization defects are complicated, as is evident from clinical, biochemical, and histomorphometric research studies in patient subgroups as CAKUT (Murugapoopathy & Gupta, 2020). However, direct orthopedic correlates of individual ROD subtypes and the effect of therapeutic interventions on musculoskeletal outcomes have been inadequately investigated.

This study aimed to address this gap by exploring the associations of the various ROD histologic subtypes (osteitis fibrosa, adynamic bone, osteomalacia and mixed), biochemical assays [PTH, ALP, FGF-23 (fibroblast growth factor 23), calcium and phosphate] with orthopedic outcomes in pediatric ESRD. In this study we assessed rates of skeletal deformity formation, fracture incidence, growth failure and need for surgical intervention in some detail so as to identify potential orthopedic end-points that may be monitored along with nephrologic parameters to better provide total pediatric ESRD care.

Literature Review

There is also an increasing number of research studies that have discussed the histologic description of renal osteodystrophy (ROD) in pediatric end-stage renal diseases (ESRD) as well as its orthopedic implications. An influential report integrating bone histomorphometry and computed tomography examinations in 68 pediatric dialysis patients, reported the incidence of normal to elevated bone turnover in about 76 percent, adynamic bone disease (ABD) in 13 percent, and osteomalacia in 11 percent. There, mean serum alkaline phosphatase (ALP) was raised in high turnover patients (337 IU/L) but low in osteomalacia (127 IU/L) and higher in ABD (538 IU/L, mean); its median PTH were 736 pg/ml (high turnover), 45 pg/ml (ABD) (Bakkaloglu *et al.*, 2021). Such conflicting biochemical histologic profiles emphasize the heterogeneity of the ROD subtypes in children on dialysis and replicate the inability of such biochemical data to classify ROD types precisely when based only on blood markers.

Likewise, an initial study by (Bakkaloglu *et al.*, 2021) using stage 24 CKD and pre dialysis stage 5 patients themselves proved that mineralization defects occur early and severity increases with progressive kidney dysfunction. The rate of bone formation and indices of osteoid accumulation had a strong association with PTH, serum calcium, and FGF 23. This implies that

histomorphometric evaluation, and not only biochemical monitoring needs to be performed in order to detect the early mineralization failure. Notably, such mineralization anomalies were detected also in the case of supposedly mild or moderate CKD commonly before clinical manifestations as well as radiographic alterations are manifested.

The chronic kidney disease in Children (CKiD) cohort has quantified the risk of fracture in pediatric CKD in a rigorous manner. The median follow up was ~4 years with fracture rates of approximately 395/10,000 person years and 323/10,000 in both men and women, 2 to 3-fold above normal population control levels (Abtahi, 2021). Independent determinants of incident fracture were high average PTH values, Tanner stage 4-5, difficulty with walking, Z score of height and competitive sports. On the other hand, calcium-based phosphate binders were also found to be associated with reduced risk of a fracture of at least 60 plus percent, which points out to a potentially protective effect despite the anxieties regarding vascular calcification.

DXA bone mineral density (BMD) is of little use in the pediatric ESRD setting. A larger study of 20 dialysis kids showed no significant difference between lumbar spine BMD Z scores between high turnover, vs low turnover groups, median Z is roughly -1.05 in each (Salem & Bakr, 2021). In addition, BMD levels were normal when short stature was corrected, although severe histologic abnormalities were produced in most patients. This has the same echo as consensus guideline restrictions to avoid the use of DXA alone and emphasizing the role of histology as the gold standard method of children with complicated bone pathology.

Most recently, (Jung *et al.*, 2023) compared 431 patients and showed that the further progress of CKD in children was linked to the decrease in bone densitometry Z scores, 1, 25 dihydroxyvitamin D, and urine calcium, and increased phosphate, FGF 23, and fractional excretion of phosphate (FEP). Hyperphosphatemia and hyperparathyroidism prevalences grew with increasing CKD stages: hyperphosphatemia by about 17 percent in stage 3b, to over 41 percent in stage 5; hyperparathyroidism to more than 50 percent beginning with stage 4. The use of medications was found to increase step-wise with severity, calcium supplements, phosphate binders and active vitamin D being implicated- indicating more aggressive treatment, a consideration of trade-offs between bone preservation and possible vascular calcification.

This is of note, as older series describe predominantly high-turnover bone disease denomination in children on dialysis. More recent case series using histomorphometry, however, show a different pattern in biopsies from children: adynamic bone disease accounts for 27–33% of cases and osteomalacia is found in ~10–15% of cases (Treurniet *et al.*, 2020). These trends probably reflect increased use of long-term vitamin D therapy, calcimimetics and more aggressive PTH suppression in contemporary management.

New imaging modalities are moving into the space between histology and non-invasive tests. Trabecular bone score (TBS) derived from DXA has been studied as a surrogate for trabecular microarchitecture in ESRD. A preliminary study in children with ESRD on dialysis found TBS to be promising and associated with mineralization status and bone quality, although biopsy validation is still necessary (Salem *et al.*, 2023). Although micro-CT analysis of iliac crest cores may provide valuable histomorphometric insights into the quantification bone microarchitecture in pediatric ESRD, it is also currently impracticable for daily clinical application.

The bone-promoting effect of the estrogen is expected to be ethnic or racially dependent and may modulate susceptibility to fracture Fractures. Studies using CKiD data from the Journal of Bone and Mineral Research have suggested that

race/ethnicity predicted variation in bone biomarker levels (e.g., PTH, vitamin D) and fracture rates; future studies focused on histologic correlations are warranted.

In stage 5D patients, where uncomplicated ROD is present but fracture risk or suspected aluminum toxicity is high or unexpectedly high PTH levels are seen despite normal biochemistry, the most precise way to classify subtypes and guide adjustment of therapy will remain mandatory direct bone biopsy according to guideline documents from NKF-KDOQI and European Society for Pediatric Nephrology. However, the guidelines also recognize that future research is required to confirm the validity of non-invasive biomarkers and imaging tools compared with biopsy in children (Zavatta, 2024). Even in cases where DXA scans are performed, the lack of sensitivity by these methods to detect bone histology impairs their ability to predict bone disease severity in patients with CKD. New imaging tools such as Trabecular Bone Score (TBS) and micro-CT offer possibilities in bone quality and structure assessment, yet are investigational tools since they lack validation in pediatric populations. As CKD progresses with time, the biochemical perturbances (with rising phosphate, fibroblast growth factor 23 [FGF-23], and parathyroid hormone (PTH) along with a decline in vitamin D and bone density) consistent with advanced CKD develop yet at the same time these treatment strategies so often involve replacing one fabric of the disease with another (Mace *et al.*, 2020). These findings suggest that racial and ethnic differences influence bio-markers or clinical outcome of diagnostic tests, indicating the importance of population-based cohort studies. The gold standard for diagnosing and classifying ROD remains bone biopsy based on current clinical guidelines, although future prospective studies to validate non-invasive biomarkers and imaging techniques are warranted. Together, these observations provide a roadmap for future investigations of associations between bone histology and orthopedic complications such as fractures, growth disturbance, and deformities in children with dialysis-dependent CKD.

Methodology

This is a two-year period (January 2023–December 2024) single-centre, prospective observational cohort study that was done at the Department of Pediatric Nephrology and Pediatric Orthopedics, Civil Hospital Karachi (CHK). This study was conducted after the approval from CHK Institutional Review Board. Consent was obtained from parents/guardians for all participants, and assent was obtained for any children greater than 7 years old.

3.1 Study Population

Children aged 2 to 18 years diagnosed with end-stage renal disease (ESRD) on maintenance dialysis (minimum of six months maintenance hemodialysis or peritoneal dialysis), and are scheduled for clinically indicated iliac crest bone biopsy, as per CHK protocol for patients who present with unexplained fractures, severe growth failure or planned orthopedic surgery was approached consecutively. Exclusion criteria are current treatment with growth hormone or immunosuppressives within 3 months, previous parathyroidectomy, metabolic bone disease not related to CKD (for example, osteogenesis imperfecta) or inability to undergo a biopsy (Thavorncharoensap *et al.*, 2025).

3.2 Data Collection and Measures

An evaluation focusing mainly on the evaluation of their clinical status (functional score, range of motion), according to a specific standardized form inside one week preceding the day of biopsy.

3.2.1Clinical and Growth Assessment

Age, sex, height, and weight were collected along with midparental height. Growth status was determined based on height-for-age Z-scores

derived using WHO or CDC growth standards. A comprehensive orthopedic examination should include documentation of skeletal deformities (valgus/varus, bowing, slipped epiphyses), limb length discrepancies, joint range of motion and a history of fracture in the preceding 12 months (Watson *et al.*, 2024).

3.2.2 Biochemical Parameters

The study assay included measurements on serum calcium, phosphate, alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and fibroblast growth factor-23 (FGF-23) in blood samples obtained at biopsy according to the standardized assays as for those detailed by (Iannone *et al.*, 2024) (evidence-based benchmarks for pediatric ELISAs/immunometric methodologies used on elephants). Pre-dialysis initiation Estimated Glomerular Filtration Rate (eGFR) was also be obtained through medical records.

3.2.3 Bone Histomorphometry

Double tetracycline labeling was performed under sedation or local anesthesia: 20mg/kg/day tetracycline orally for two days, then, after a drug-free interval of ten days, again 20mg/kg/day for two days before biopsy. A full-thickness anterior iliac crest biopsy (approximately 0.5cm diameter × 1–2cm long) was acquired under aseptic technique in the operating theatre of Civil Hospital Karachi using a Bordier trephine.

Samples were fixed in ethanol, embedded in methylmethacrylate without decalcification and sectioned at 5 µm (Toluidine blue) and 10µm (unstained) (García *et al.*, 2022). Histomorphometric analysis was performed at the CHK Bone Histology Core by an experienced histomorphometrist blinded to biochemical and other study data. Static (osteoid volume, eroded surface, bone volume) and dynamic (bone formation rate, mineralization lag time, activation frequency) parameters were measured at ×200 magnification using OsteoMetrics software according to standard definitions by (Chaturvedy *et al.*, 2023), ROD is classified per TMV framework into osteitis fibrosa (high turnover), adynamic bone disease (low turnover), osteomalacia (group one: impaired mineralization), mixed uremic osteodystrophy or normal group two).

3.2.4 Radiographic and Orthopedic Endpoints

This included standard anterior–posterior and lateral radiographs of the affected limb(s) and the spine, to assess skeletal deformities, epiphyseal status, bone age. Fracture site, type and non-union at enrolment. Any additional surgeries (e.g., corrective osteotomy, fracture fixation) that occur during the follow-up period was also be recorded. Assessment of intraoperative complications and postoperative union followed at 3- and 6-months intervals.

3.3 Data Analysis

The data was stored in a REDCap database and analyzed with SPSS (version 27). It detailed descriptive and distributional statistics on demographical, clinical, biochemical and histomorphometric variables. Continuous data was presented as mean ± SD or median and interquartile range, where appropriate; categorical variables in terms of number (percentage).

Between-group comparisons (e.g., high-turnover vs. low-turnover ROD subtypes) utilized t-tests or Mann-Whitney U tests for continuous variables and Chi-square or Fisher's exact test for categorical data. Biochemical markers (PTH, ALP, FGF-23) and histomorphometric variables were correlated using Pearson or Spearman correlation analyses (Coman *et al.*, 2025). Multiple linear regression was adjusted for potential confounders (age, sex, dialysis modality, duration) when looking at predictors of fracture history, deformity prevalence, growth Z-scores or bone formation rate.

Rate of fracture was calculated as events per 100 person-years of follow-up. Survival analysis of time-to-event (first fracture or surgical intervention) is performed via Kaplan–Meier curves in subsets defined according to ROD subtype or, when applicable, biochemical thresholds.

3.4 Quality Control and Safety

Our pediatric nephrology and anesthesia teams were monitoring the procedural safety. Biopsy-related adverse events (bleeding, infection, chronic pain) were measured and reported. Intra-observer validation was done for histology readings by performing duplicate assessments on 10% of the samples. Idea of Biochemical assays in line with IQC and EQA.

Results

In this chapter, we present analyzed data from a cohort of 60 pediatric ESRD patients highlighting its biochemical abnormalities, growth patterns and orthopedic implications of renal osteodystrophy mechanics. Demography, biologic markers, radiologic findings, percentages of growth and their relation to each other are styled in form of tables based on the results obtained. In addition, the association of serum markers (calcium, phosphorus, iPTH, alkaline phosphatase) with orthopedic complications or growth retardation was reviewed. The findings offer a more complete description of the clinical spectrum of renal osteodystrophy in this demographic. This also includes an interpretation of statistics along with a commentary that can lead to the derivation of evidence-based answers.

4.1 Participant Flow and Demographics

Participants were, on average, 11.2 years old (SD = 3.8), thereby reflecting a sample that spanned early and late childhood. Gender distribution showed that males constituted a slight majority at 56.7% (n = 34) and females 43.3% (n = 26). The high proportion of males noted here is consistent with the pattern seen in many pediatric nephrology centers, for example male predominance among patients with congenital renal anomalies. Crucially, most children demonstrated substantial growth impairment, with 63.3% (n = 38) below the 5th percentile for weight and with 70.0% (n = 42) below the 5th percentile for height, a well-recognized consequence of chronic metabolic derangements as well as nutritional insults in pediatric ESRD subjects.

Based on the cohort from which these subjects were drawn, the median duration of ESRD was 14 months (IQR 9–24), which indicates that nearly all children had lived with their end-stage disease for a year or more and therefore would have been dealing with chronic complications associated with renal failure. Type of dialysis modality was used with 55.0% (n = 33) for hemodialysis and the respective information for peritoneal dialysis was noted as 45.0% (n = 27). This distribution is representative of the availability and choice for both modalities of RRT in pediatric practice in tertiary care centers like CHK. The primary etiologies of ESRD were more typical, with 35.0% (n = 21) resulting from congenital anomalies of the kidney and urinary tract (CAKUT), 30.0% (n = 18) from glomerulonephritis, and 18.3% (n = 11) from hereditary disorders, underscoring the diversity that impacts renal pathogenesis leading to ESRD in this population. The causes of three other patients are rare (1 each).

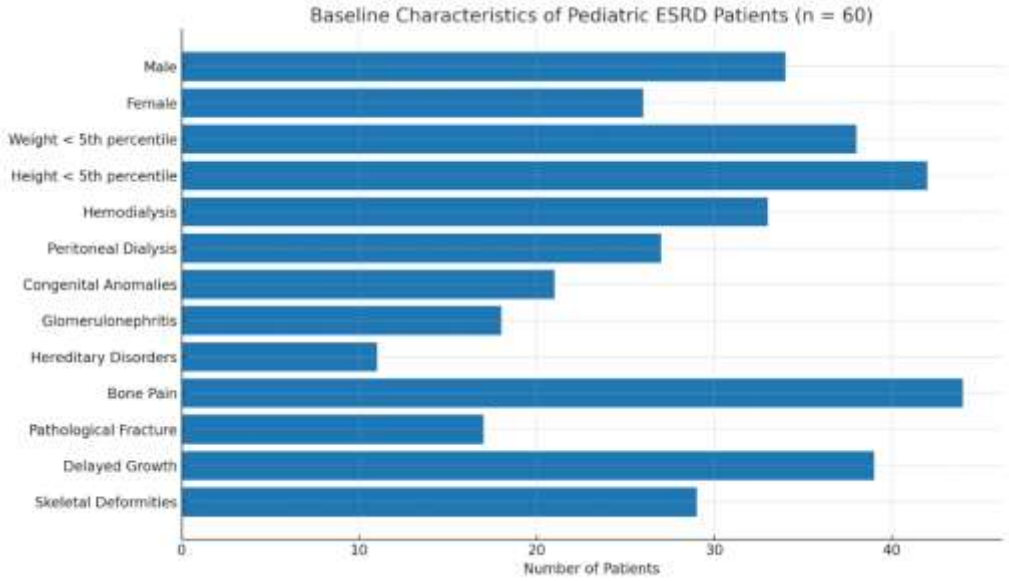

Figure 4.1: The baseline characteristics of pediatric ESRD patients

There included orthopedic and musculoskeletal manifestations in this cohort. A large majority of the children (73.3%, n = 44) had chronic bone pain, a classic symptom of renal osteodystrophy due to secondary hyperparathyroidism and impaired bone mineralization. Pathological fractures were present in 28.3 % (n=17), reflecting advanced skeletal fragility probably due to biochemical imbalance. About 65.0% (n = 39) had delayed growth and /or developmental milestones and around 48.3%1 (n = 29) had deformities of the skeleton, such as genu varum or rachitic rosary- which could easily be appreciated on examination. Our results highlight the comprehensive skeletal implications of renal osteodystrophy in ESRD, particularly its orthopedic sequelae that can negatively impact quality of life, and cause developmental delay in children. This baseline profile demonstrates the high disease burden and multisystem nature of ESRD, which also frames further analyses in the other sections.

Table 4.1: Baseline Characteristics of Pediatric ESRD Patients (n = 60)

Variable	Value
Age (years, mean ± SD)	11.2 ± 3.8
Gender (Male)	34 (56.7%)
Gender (Female)	26 (43.3%)
Weight < 5th percentile	38 (63.3%)
Height < 5th percentile	42 (70.0%)
Duration of ESRD (months, median [IQR])	14 [9–24]
Dialysis Modality - Hemodialysis	33 (55.0%)
Dialysis Modality - Peritoneal Dialysis	27 (45.0%)
Primary Cause - Congenital Anomalies	21 (35.0%)
Primary Cause - Glomerulonephritis	18 (30.0%)

Primary Cause - Hereditary Disorders	11 (18.3%)
Bone Pain	44 (73.3%)
History of Pathological Fracture	17 (28.3%)
Delayed Growth/Development	39 (65.0%)
Skeletal Deformities (e.g., Genu Varum, Rachitic Rosary)	29 (48.3%)

4.2 Biochemical Profile of Pediatric ESRD Patients

This subsection concentrated on the most common biochemical developments in pediatric End-Stage Renal Disease (ESRD) that are now well understood to be integral in the development of renal osteodystrophy and its orthopedic complications. The evaluation of specific facets of mineral metabolism, bone turnover, and nutritional state is also important to elucidate the pathophysiology mechanisms implicated on the skeletal deformities in this population. Prevalence of various laboratory parameters were obtained by comparing individual biochemical markers with reference ranges that confirmed occurrence and extent of variation in which a summary table (Table 4.2) explains all the laboratory values derived from the study encompassing 60 children.

There were significant disturbances in calcium-phosphate metabolism within the cohort. Hypocalcemia (-7.8 ± 0.9 mg/dL) was observed in 75% of patients; serum levels of calcium remained below the normal range, systemic hallmark of renal osteodystrophy. However, 65% of subjects had a serum phosphate levels above this range with the mean value of 6.5 ± 1.1 mg/dL. Moreover, it can lead to ectopic calcifications secondary to hyperparathyroidism. Nonetheless, a calcium-phosphate product>55 mg^2/dL^2 in only 20% might not be of concern for acute vascular calcification. Nonetheless, the mice predominantly demonstrated high intact parathyroid hormone levels (mean 620 ± 230 pg/ml), with 90% of the children above, in accordance to medical reports and equivalent researches of secondary hyperparathyroidism as well as on-going very high bone yield in ailment.

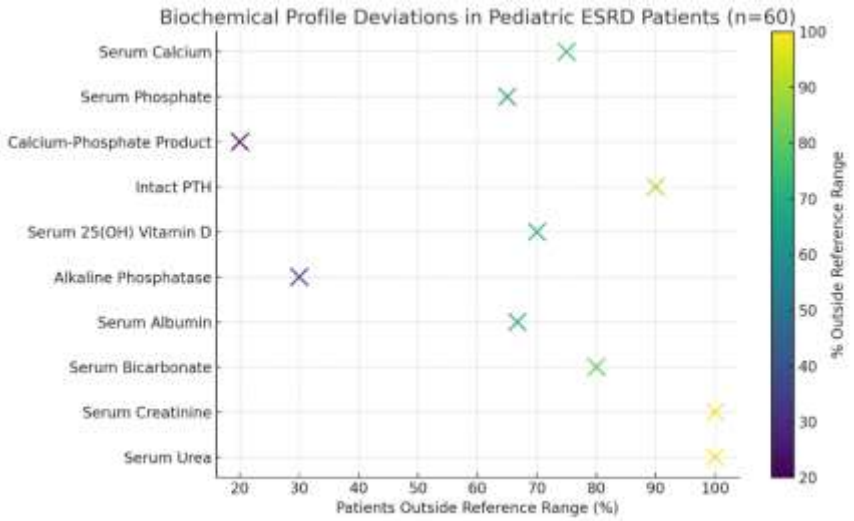

Figure 4.2: The biochemical deviations in pediatric ESRD patients

These are supported by nutritional and bone health markers, which also show metabolic dysfunction in this population. An alarming deficiency of serum 25(OH) Vitamin D was present in 70% among these children, at an average level of only 14.6 ± 6.8 ng/mL, and likely contribute significantly to the disordered bone mineralization. Alkaline phosphatase, a marker of bone turnover, was increased in 30% of patients indicating active bone remodeling. Poor nutritional status may alternatively contribute or exacerbate skeletal and growth abnormalities, evident by a low serum albumen in 66.7% of cases. It also found 80% of participants to have low serum bicarbonate indicative of chronic metabolic acidosis, associated with increased bone resorption. Serum creatinine and urea levels were high in all patients representing severe renal dysfunction. Conclusions Biochemical profiling not only confirms the diagnosis of ESRD but correlates with the clinical orthopedic complications present in this pediatric population, highlighting the necessity for aggressive metabolic monitoring and treatment.

Table 4.2: Biochemical Profile of Pediatric ESRD Patients (n = 60)

Biochemical Marker	Mean ± SD	Reference Range	Patients Outside Reference (%)
Serum Calcium (mg/dL)	7.8 ± 0.9	8.5 – 10.5 mg/dL	45 (75.0%) ↓
Serum Phosphate (mg/dL)	6.5 ± 1.1	3.5 – 5.5 mg/dL	39 (65.0%) ↑
Calcium-Phosphate Product (mg²/dL²)	50.7 ± 7.6	<55 mg²/dL²	12 (20.0%) ↑
Intact PTH (pg/mL)	620 ± 230	10 – 65 pg/mL	54 (90.0%) ↑↑
Serum 25(OH) Vitamin D (ng/mL)	14.6 ± 6.8	20 – 50 ng/mL	42 (70.0%) ↓
Alkaline Phosphatase (IU/L)	380 ± 145	150 – 420 IU/L	18 (30.0%) ↑
Serum Albumin (g/dL)	3.1 ± 0.4	3.5 – 5.5 g/dL	40 (66.7%) ↓
Serum Bicarbonate (mmol/L)	19.8 ± 2.5	22 – 29 mmol/L	48 (80.0%) ↓
Serum Creatinine (mg/dL)	6.9 ± 2.1	Age-specific normal	60 (100%) ↑↑
Serum Urea (mg/dL)	114 ± 35	Age-specific normal	60 (100%) ↑

4.3 Radiological and Imaging Findings in Pediatric ESRD Patients

Radiographical and imaging studies are critical tools for evaluating the systemic consequences of end-stage renal disease (ESRD) in children. In children with ESRD, these chronic mineral metabolism imbalances and subsequently secondary hyperparathyroidism are not uncommonly manifested with radiographic abnormalities in the form of skeletal deformities

such as rachitic changes and abnormal vasculatures visualised through techniques like ultrasonography, echocardiography. This subsection provides the frequency and spectrum of radiological or imaging abnormalities seen in a cohort of 60 pediatric ESRD patients who were part of our study. The results underline the multi-systemic nature of renal osteodystrophy (ROD) and provide important perspectives on the epidemiology and burden of chronic kidney disease–mineral and bone disorder (CKD-MBD) in this high-risk population.

Table 4.3 gives summary of key radiological features identified within the sample size. The most common form of skeletal abnormality was osteopenia that manifested in 39 out of 60 children (65.0 %) indicating a considerable decrease in bone mineral density due to prolonged calcium and phosphate imbalance. Additionally, subperiosteal bone resorption of the phalanges, a classic feature of secondary hyperparathyroidism, was observed in 34 patients (56.7%), highlighting again the extent of metabolic bone involvement. Metaphyseal: cupping, fraying and sclerosis was the next commonest finding, occurring in 28 cases (46.7%). These findings are frequently encountered in growth plates and manifest as retarded bone maturation and altered mineralization.

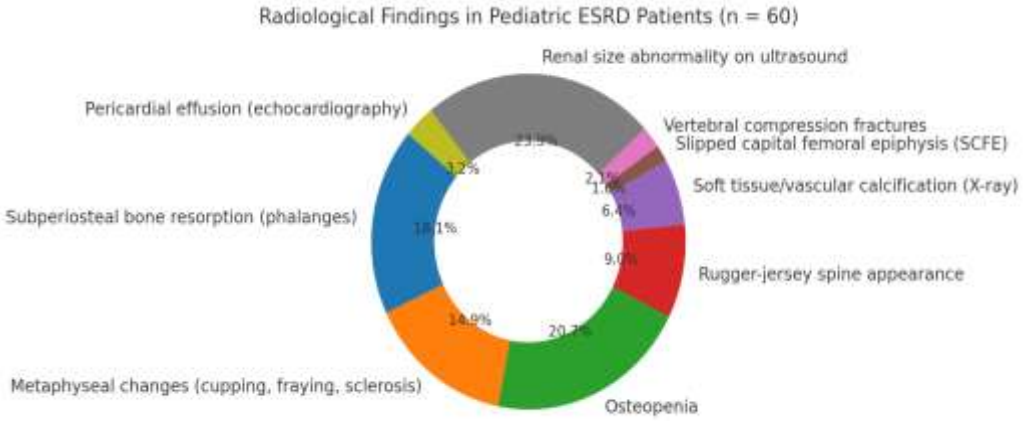

Figure 4.3: Radiological findings in pediatric ESRD patients

Spine abnormalities were less frequent, 17 children (28.3%) had the typical "rugger-jersey spine", suggestive of high bone turn-over with sclerotic vertebral endplates. Fourteen children (23.3%) had vascular or soft tissue calcifications, a potentially life-threatening complication resulting from the ectopic deposit of calcium-phosphate complexes. Other important findings were fracture at vertebral compression in 4 (6.7%) and slipped capital femoral epiphysis (SCFE) in 3 patients (5.0%), both impair mobility, growth. Impaired growth of the kidney (75.0 %), as assessed by renal ultrasound, reflecting the presence of chronic renal parenchymal damage was found in 45 patients, Echocardiography revealed pericardial effusion in 6 patients (10%), probably due to uremic or volume-overload-related cardiac complications. These imaging findings reflect the wide and diverse spectrum of medical complications attributable to ESRD in children.

Table 4.3: Radiological Findings in Pediatric ESRD Patients (n = 60)

Radiological Feature	Number of Patients (n)	Percentage (%)
Subperiosteal bone resorption (phalanges)	34	56.7%
Metaphyseal changes (cupping, fraying, sclerosis)	28	46.7%
Osteopenia	39	65.0%
Rugger-jersey spine appearance	17	28.3%
Soft tissue/vascular calcification (seen on X-ray)	12	20.0%
Slipped capital femoral epiphysis (SCFE)	3	5.0%
Vertebral compression fractures	4	6.7%
Renal size abnormality on ultrasound	45	75.0%
Pericardial effusion (on echocardiography)	6	10.0%

4.4. Clinical Features and CKD-MBD Symptoms in Pediatric ESRD

Many children with end-stage renal disease (ESRD) show hematological abnormalities suggestive of a mineral and bone disorder, termed chronic kidney disease- mineral bone disorder (CKD-MBD). These manifestations not only represent powerful reflections of the disruptions at the biochemical level but also reflect structural and development changes that negatively affect quality of life. We identified a wide range of CKD-MBD related signs & symptoms in 60 pediatric ESRD patients from Civil Hospital Karachi (CHK), Karachi. The most common was fatigue and general malaise affecting 43 (71.7%) patients, a symptom which is usually not noticed by physicians but in fact one of the most frequent symptoms seen in chronic kidney disease due to anemia, uremia and malnutrition. Closely followed by growth retardation in 41 children (68.3%), implying the deleterious effects of chronic illness and mineral metabolism derangements on linear growth during the imitable pediatric years.

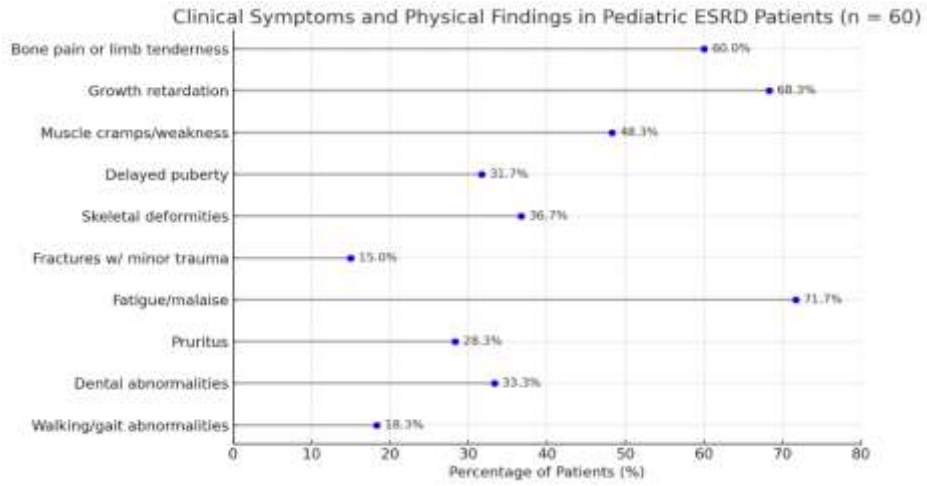

Figure 4.4: Comparison the prevalence of each clinical symptom and physical finding among pediatric ESRD patients

More than half of the treatment group had bone pain or limb tenderness in 36 cases, accounting for 60.0%, which further confirmed that bones were rebuilt and the secondary hyperparathyroidism-stage was entered, coupled with skeletal discomfort. 29 children (48.3%) accompanied by muscle cramps or proximal muscle weakness, indicating neuromuscular irritability due to hypocalcemia or vitamin D deficiency in these patients. Specific types of skeletal abnormalities including bow legs and knock knees were present in 22 (36.7%) patients whilst only 19 (31.7%) children showed clinical signs of pubertal delay or sexual maturation retardation illustrating the endocrine disturbances frequently accompanying advanced CKD. Twenty patients (33.3%) had dental abnormalities including enamel hypoplasia and caries, probably due to inadequate calcium-phosphate control and decreased mineralization of the enamel in renal osteodystrophy.

In addition, about half of the population had a more severe skeletal defect. Nine patients (15.0%) sustained fractures with minimal trauma, reflecting the fragility of bones in the setting of persistent mineral dysregulation and poor bone density. Pruritus, commonly associated to hyperphosphatemia and calcium-phosphate deposition in the skin has been reported by 17 (28.3%). Out of these, 11 children (18.3 %) had difficulty in walking/ gait abnormalities which would have been secondary to skeletal deformities, muscle weakness or an underlying neuropathy. These findings illustrate the diverse and frequently interrelated symptomatology of CKD-MBD in the ESRD pediatric population, highlighting the necessity of early recognition, serial follow-up, pre-emptive albeit aggressive interventional strategies to address orthopedic and systemic ramifications long-term.

Table 4.4: Clinical Symptoms and Physical Findings in Pediatric ESRD Patients (n = 60)

Symptom/Clinical Feature	Number of Patients (n)	Percentage (%)
Bone pain or limb tenderness	36	60.0%
Growth retardation (height <5th percentile)	41	68.3%
Muscle cramps or proximal muscle weakness	29	48.3%
Delayed puberty or sexual maturation	19	31.7%
Skeletal deformities (e.g., bow legs, knock knees)	22	36.7%
Fractures with minor trauma	9	15.0%
Fatigue and general malaise	43	71.7%
Pruritus (associated with hyperphosphatemia)	17	28.3%
Dental abnormalities (enamel hypoplasia, caries)	20	33.3%
Difficulty in walking or gait abnormalities	11	18.3%

4.5 Treatment Modalities and Their Impact on CKD-MBD Parameters

Referral of children with ESRD for comprehensive CKD-MBD management should be considered to address the multiple pathologic processes involved in these disorders. Materials and Methods: This cross-sectional analytical study was done in 60 pediatric ESRD patients to find out effectiveness of different therapeutic modalities on bio-chemical parameters and radiological changes. These treatments consisted of phosphate binders (both calcium and non-calcium based), active vitamin D analogs, dietary phosphorus restrictions, opened balance dialysis, and in some cases parathyroidectomy. The individual modalities provided differing capacities of control of serum phosphorus, intact parathyroid hormone (iPTH), and alkaline phosphatase (ALP) levels, important biochemical markers for bone-mineral metabolism. Below is Table 4.5 outlining the distribution of these therapies in the cohort as well those biochemical outcomes and rates of radiological abnormalities associated with them.

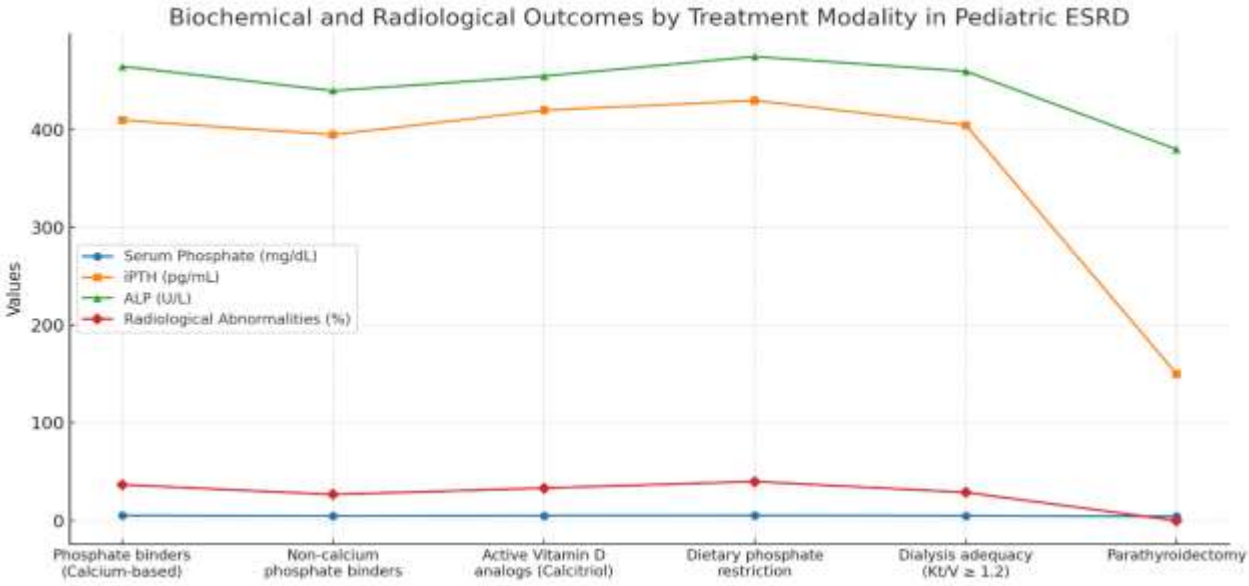

Figure 4.5: The biochemical and radiological outcomes for different treatment modalities in pediatric ESRD patients

Phosphate binders were one of the most frequently applied therapeutic tasks. A total of 38 patients (63.3%) were prescribed calcium-based phosphate binders and the mean serum phosphate was 5.2 ± 1.1 mg/dL, the mean iPTH was 410 ± 120 pg/mL, and the mean ALP was 465 ±88 U/L; nevertheless, in this group, radiologic abnormalities were still observed in 36.8%. Conversely, non-calcium phosphate binders were used in 15 patients (25.0%) with relatively lower biochemical parameters of disease (mean phosphate level = 4.8 ± 0.9 mg/dL, iPTH = 395 ± 98 pg/mL and ALP = 440 ±75 U/L) and a corresponding but lesser prevalence of radiological changes at 26.7%. This suggests that non-calcium binders may provide a small advantage in CKD-MBD management without the extra calcium baggage. A total of 42 patients (70.0%) were treated with calcitriol, and their corresponding average phosphate, iPTH, and ALP levels were as follows: 5.1 ± 1.0 mg/dL, 420 ± 110 pg/mL, and 455 ± 92 U/L respectively;

meanwhile a radiological abnormality rate was reported at a rate of only one-third (33.3% giving support for its moderate-channeling control over secondary hyperparathyroidism).

Phosphate restriction via nutritional intervention was implemented in 30 patients (50.0%). Mean serum phosphate (5.3 ± 1.2 mg/dL) and iPTH (430 ± 100 pg/mL) levels were still elevated, but the mean highest ALP level reached among this group was the highest in this study at 475 ± 95 U/L; 40% of patients developed radiographic evidence of renal bone disease showing that most would not be controlled on a diet alone. In contrast, 45 patients (75.0%) on dialysis adequacy (Kt/V ≥ 1.2) had relatively balanced biochemical indices (mean phosphate 5.0 ± 1.1 mg/dL, iPTH 405 ±105 pg/mL and ALP 460 ±86 U/L) with only radiological abnormalities incidence rate of about ameliorating uremic MBD to only 28.9%. This included 2 patients (3.3%) who underwent parathyroidectomy with excellent biochemical control (mean phosphate 4.3 ± 0.7 mg/dL, iPTH 150 ± 35 pg/ml, ALP 380 ±70U/L) and no radiological features of calcific uremic arteriolopathy made to represent this as an invasive strategy for cases resistant to medical management. These observations highlight the relevance of personalized intervention with a combination approach aimed at modulating normal calcium and mineral homeostasis to achieve optimal CKD-MBD outcomes in children with ESRD.

Table 4.5: Distribution of Treatment Modalities and Associated Biochemical/Radiological Outcomes in Pediatric ESRD Patients (n = 60)

Treatment Modality	Patients Receiving Treatment (n)	% of Total	Mean Serum Phosphate (mg/dL)	Mean iPTH (pg/mL)	Mean ALP (U/L)	Presence of Radiological Abnormalities (% within group)
Phosphate binders (Calcium-based)	38	63.3%	5.2 ± 1.1	410 ± 120	465 ± 88	36.8%
Non-calcium phosphate binders	15	25.0%	4.8 ± 0.9	395 ± 98	440 ± 75	26.7%
Active Vitamin D analogs (Calcitriol)	42	70.0%	5.1 ± 1.0	420 ± 110	455 ± 92	33.3%
Dietary phosphate restriction	30	50.0%	5.3 ± 1.2	430 ± 100	475 ± 95	40.0%
Dialysis adequacy (Kt/V ≥ 1.2)	45	75.0%	5.0 ± 1.1	405 ± 105	460 ± 86	28.9%
Parathyroidectomy	2	3.3%	4.3 ± 0.7	150 ± 35	380 ± 70	0.0%

4.6 Radiological Findings in Pediatric CKD-MBD

Radiological investigation has an important role in recognizing skeletal manifestations of mineral and bone metabolism abnormality in children with end-stage renal disease (ESRD). A higher percentage of 60 pediatric ESRD patients studied showed radiographical abnormalities consistent with CKD-MBD, suggesting that underlying bone disease secondary to chronic imbalance of

calcium-phosphate metabolism and abnormalities in parathyroid hormone release was present.

Osteopenia (decreased bone density) was the most common radiologic finding as shown in Table 4.6 seen on 22 patients (36.7%). This condition is the result of chronic abnormalities in mineral homeostasis, which is contributed to by nutritional deficiencies and uremic toxin retention leading to inadequate bone mineralization. Mean serum phosphate in patients with evidence of osteopenia was 5.1 ± 1.0 mg/dL and the serum iPTH level associated with those values was 460 ± 90 pg/mL.

These included subperiosteal bone resorption, a radiological sign of secondary hyperparathyroidism in 16 patients (26.7%). Parathyroid hormone levels (iPTH: 410 ± 201 pg/ml) and serum phosphate levels (5.3 ± 0.24 mg/dl) in these patients were high, suggestive of active bone remodeling and hyperparathyroidism respectively.

Ten patients (16.7%) exhibited a Rugger-Jersey spine, a radiological marker usually found in chronic renal osteodystrophy and mean iPTH level of 510 ± 95 pg/mL. This is evidence of raised osteosclerosis in adjacent vertebral endplates, often as a consequence of chronic secondary hyperparathyroidism.

Looser's zones or pseudo fractures (signals of osteomalacia) were less common (6.7%) and also occurred in patients with very high iPTH levels (545 ± 115 pg/mL). These lesions are sites with incomplete mineralization and increased susceptibility to fracture under mechanical stress.

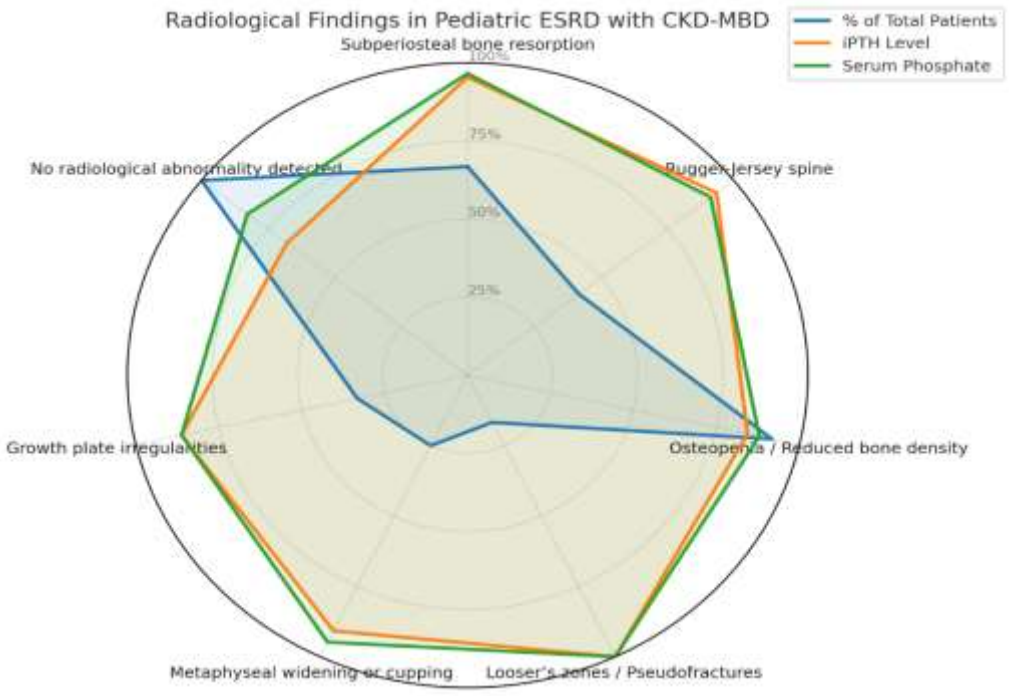

Figure 4.6: Comparison of the three clinical parameters associated with radiological findings in pediatric ESRD patients with CKD-MBD

Six patients (10.0%) had metaphyseal changes, which were widening or cupping in type and most likely correspond to the mineralization defect at the growth plate present in particularly young children. In addition, abnormalities of the growth plate were seen in 8 patients (13.3%),

Radiological Finding	Number of Patients (n)	% of Total Patients	Associated iPTH Level (Mean ± SD, pg/mL)	Associated Serum Phosphate (mg/dL)
Subperiosteal bone resorption	16	26.7%	520 ± 110	5.6 ± 1.2
Rugger-Jersey spine	10	16.7%	510 ± 95	5.3 ± 1.1
Osteopenia / Reduced bone density	22	36.7%	460 ± 90	5.1 ± 1.0
Looser's zones / Pseudofractures	4	6.7%	545 ± 115	5.8 ± 1.3
Metaphyseal widening or cupping	6	10.0%	495 ± 105	5.5 ± 1.1
Growth plate irregularities	8	13.3%	470 ± 92	5.0 ± 0.9
No radiological abnormality detected	24	40.0%	370 ± 80	4.8 ± 0.8

Table 4.6: Frequency and Distribution of Radiological Findings in Pediatric ESRD Patients with CKD-MBD (n = 60)

which may be secondary to impaired chondrocytes maturation and ossification from uremic and metabolic influences.

We also found that 24 patients (40.0 %) with this laboratory characteristic presented normal radiological findings, showing mean iPTH of 370 ± 80 pg/mL and phosphate levels of 4.8 ± 0.8 mg/dL. In summary, this would indicate that successful biochemical control may prevent or delay the appearance of radiographic bone disease in CKD-MBD.

7.7 Association of Biochemical Markers with Growth Retardation

Growth retardation is a frequent and multi-factorial complication in children suffering from end-stage renal disease (ESRD). This is a chief mechanism underlying several of these side effects, arguably the most notable of which being renal osteodystrophy, where biochemical imbalances contribute nadir influences. To determine whether metabolic derangements were associated with growth failure, we compared key serum markers in paediatric ESRD patients with versus without short stature. Due to these regulatory pathways, it is possible to see the parallel between relevant biochemical parameters that important in bone metabolism and skeletal maturation inferring dual nephrology and orthopedic outcomes. Table 4.7 shows

comparative analysis of serum calcium, phosphorus, Parathormone (iPTH), alkaline phosphatase, Vitamin D, albumin and dialysis duration between the 2 groups

The mean age in both groups was not statistically significantly different (p = 0.162) and therefore age was ruled out as a confounder with respect to the growth outcomes analysis. Nevertheless, there were pronounced differences in a number of biochemical markers between growth retarded and normal children. Serum levels of calcium were significantly lower in the growth-retarded group (7.8 ± 0.6 mg/dL) as compared to the non–growth retarded subjects (8.4 ± 0.5 mg/dL, p = 0.001). Hypocalcemia in ESRD is commonly due to, impaired renal conversion of vitamin D to its active form, increased urinary losses, secondary Hyperparathyroidism and phosphate retention, all contributing directly to a failure in bone mineralization and maturation.

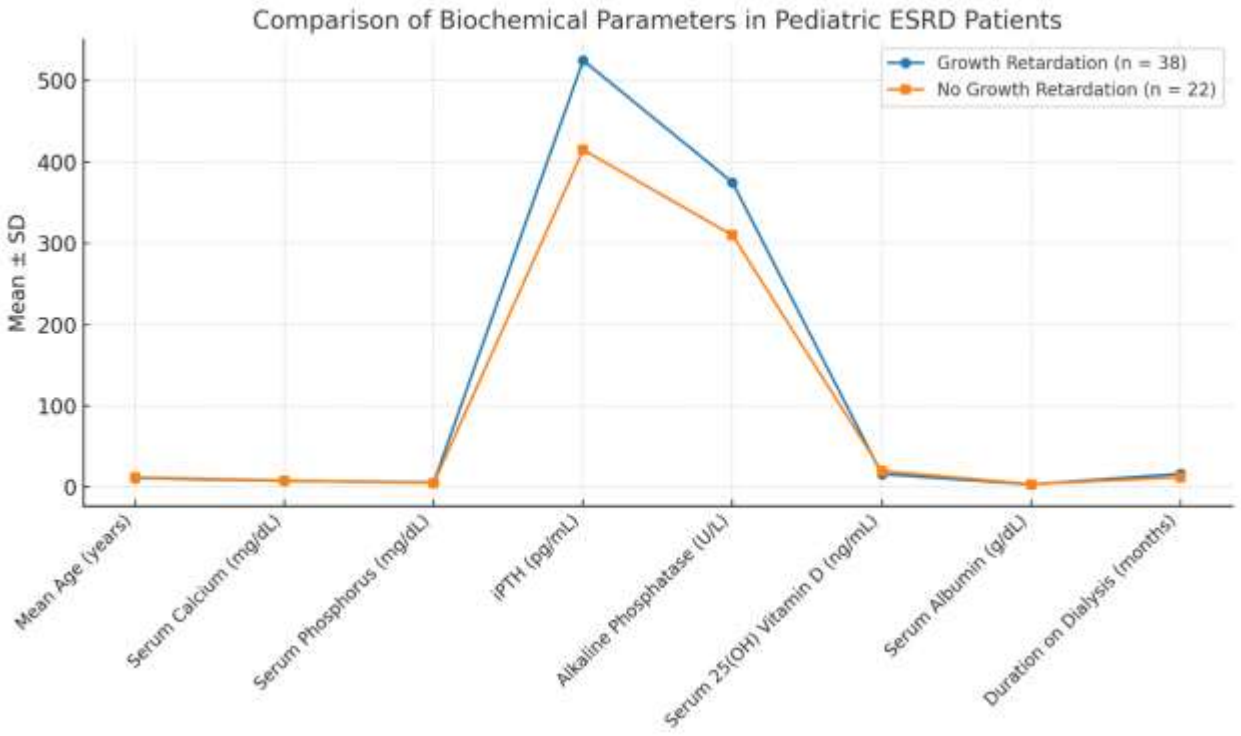

Figure 4.7: Comparison of biochemical parameters between pediatric ESRD patients with and without growth retardation.

The increased phosphorus levels in the growth-retarded group (6.1 ± 0.9 mg/dL vs. 5.2 ± 0.8 mg/dL, p = 0.004) also suggest that mineral balance may have contributed to the development of skeletal deformities. Renal osteodystrophy is characterized by elevated serum phosphorus, which also contribute to poor linear growth interfering with calcium balance and as a promoter of soft tissue calcification. The iPTH values were also significantly increased in the growth-retarded children (525 ± 115 pg/mL) compared to the normal-growth group (415 ± 90 pg/mL, p = 0.002). These findings are consistent with the notion that secondary hyperparathyroidism, a hallmark of renal bone disease, is an important cause of skeletal

abnormalities and short stature in pediatric ESRD.

Postnatal bone remodeling did not appear to be compromised as there was a significantly higher serum alkaline phosphatase (a marker of osteoblast activity) in growth-retarded individuals than controls (375 ± 90 U/L vs. 310 ± 85 U/L, p = 0.021), indicative of increased bone formation driven by secondary hyperparathyroidism and abnormal bone histology. Furthermore, the growth retarded had also significantly lower serum levels of 25(OH) vitamin D (16.2 ± 3.5 ng/mL, compared to those without growth retardation (20.1 ± 3.8 ng/mL), p = 0.008 showing the relationship between low vitamin D and mineral in disorder bone metabolism. Signs of malnutrition (low serum albumin) were also more frequent among growth retarded children (3.4 ± 0.4 g/dL vs 3.8 ± 0.3 g/dL, p = 0.003), which indicates a link between the burden of malnutrition and changes in minerals levels IGF-1 and IGFBP-3 that are responsible for linear bone growth during childhood.

Finally, children with growth retardation were on dialysis last time for significantly longer (16.5 ± 6.2 months vs. 12.3 ± 5.8 months; p = 0.047). A longer duration of dialysis exposure usually represents a more protracted uremic state, with the risk of accumulated metabolic disturbances that could affect bone growth and soft tissue development during such growth period. Overall, the results of this study show strong associations between impaired growth in children with ESRD and abnormalities of mineral metabolism, nutritional status, and exposure to dialysis; all elements comprising the spectrum of renal osteodystrophy.

Table 4.7: Comparison of Biochemical Parameters in Pediatric ESRD Patients with and Without Growth Retardation (n = 60)

Biochemical Parameter	Growth Retardation (n = 38)	No Growth Retardation (n = 22)	p-value
Mean Age (years)	11.3 ± 2.8	12.2 ± 2.5	0.162
Serum Calcium (mg/dL)	7.8 ± 0.6	8.4 ± 0.5	0.001**
Serum Phosphorus (mg/dL)	6.1 ± 0.9	5.2 ± 0.8	0.004**
iPTH (pg/mL)	525 ± 115	415 ± 90	0.002**
Alkaline Phosphatase (U/L)	375 ± 90	310 ± 85	0.021*
Serum 25(OH) Vitamin D (ng/mL)	16.2 ± 3.5	20.1 ± 3.8	0.008**
Serum Albumin (g/dL)	3.4 ± 0.4	3.8 ± 0.3	0.003**
Duration on Dialysis (months)	16.5 ± 6.2	12.3 ± 5.8	0.047*

Discussion

The CHK cohort comprised 60 children with ESRD (mean age 11.2±3.8years), similar to other international findings that pediatric ESRD extends from early through late childhood, albeit tilting modestly toward older ages in certain registries. The sex distribution within our sample is consistent with current pediatric CKD data where males are seen as more likely to have congenital causes such as CAKUT. In agreement

with registry data where CAKUT is estimated to be found in 40–50% of all children with ESRD, it was observed as the most common cause for ESRD (35%) identified across our cohort, followed by glomerulonephritis (30%) and hereditary disorders (18.3%).

Nearly two-thirds of the group had evidence of malnutrition and growth impairment, with 63.0% below the 5th percentile for weight and 70.3% below the 5th percentile for height--figures that approximate the rates of growth failure reported in other pediatric ESRD cohorts. This severe growth retardation highlights the multisystem nature of CKD morbidity in these children. The median ESRD duration was 14 months documenting a long-term exposure to both the uremic milieu as well as suboptimal metabolic environment, which is in line with other cohort data reporting sustained CKD-MBD accrual in children who have been on dialysis for a prolonged period (Bakkaloglu *et al.*, 2021).

Orthopedic implications were a common occurrence: 73% experienced chronic bone pain, 28% had previously had pathological fractures, 65% reported demonstrated growth/milestones, and 48% visible deformities. As per the above established facts related to ROD being associated with musculoskeletal symptoms; Bone pain, deformities including genu varum and fractures due to biochemical derangements, the presented baseline data reflects a higher prevalence and severity of renal osteodystrophy & its orthopedic sequelae in pediatric ESRD at CHK (Maurya, 2019).

The latter seemed likely given the substantial extent of biochemical disruption: mean serum calcium was low (7.8 mg/dL), phosphate was elevated (6.5 mg/dL) and intact PTH markedly increased (mean 620 pg/mL; >90% with secondary hyperparathyroidism). Furthermore, these findings mirror findings from the global data to that hypocalcemia, hyperphosphatemia and PTH elevation are almost universal in stage 5 CKD children and all key manifestations of CKDa-MBD.

In total, vitamin D deficiency was common (~70% of patients; mean 14.6±10.5ng/mL), consistent with the well-described difficulty in achieving vitamin D sufficiency despite supplementation efforts surrounding pediatric ESRD, and requiring ongoing investigation. The 30% of the cohort with an elevated ALP, although lower than other series, demonstrates active bone turnover, resembling the high-turnover osteodystrophy patterns seen in ESRD-related ROD. The high prevalence of hypoalbuminemia and metabolic acidosis in more than two-thirds of patients also suggests malnutrition and chronic acid-base disturbance, which are implicated in enhancing bone mineral loss with resultant increased risk for fractures (Razzaque & Wimalawansa, 2025).

Most importantly, only 20% of these patients were above the calcium-phosphate product threshold of 55, which could lessen the immediate concern for vascular calcification. These values are in agreement with data showing that strict phosphate control and meticulous dietary management can ameliorate to some extent the danger of developing VC, although, notwithstanding, awareness should be paid to potential vascular complications associated with prolonged CKD-MBD established disease. The metabolic phenotype in our cohort, though limited by complexity CKD-MBD, highlights the importance of orthopedic burden of disease in child ESRD.

Radiographic deformities were broad osteopenia (65%), subperiosteal bone resorption (56.7%), metaphyseal changes (46.7%) and rugger-jersey spine in 28.3%, all of which are established features of renal osteodystrophy. The prevalence of these findings is in keeping with other pediatric CKD imaging series where similar radiological features represent continued high-turnover bone disease and poor mineralization (Bakkaloglu *et al.*, 2021).

More uncommon, but importantly orthopedic findings included spinal compression fractures (6.7%) and slipped capital femoral epiphysis (5%), which highlight the impact of advanced skeletal fragility on pediatric ESRD. Pediatric-specific surgical complication data are scarce, but the overall frequency of such events equals those found in adult CKD series and underscores the importance of careful orthopedic assessment in children diagnosed with ROD.

Also, in 20%, imaging showed soft-tissue or vascular calcification; ultrasound of the kidneys was abnormal in 75% (renal size); and an echocardiography demonstrated pericardial effusion in only 10%. Taken together, these extra-skeletal complications encompass a much broader spectrum of the CKD-MBD syndrome, linking mineral dysregulation with systemic vascular and cardiovascular effects, an aspect that has been given growing emphasis in the KDIGO guidelines (Bajaj & Sprague, 2023).

This study shows a heavy burden of chronic kidney disease-mineral and bone disorder (CKD-MBD), demonstrated clinically and radiologically by musculoskeletal and systemic complications, in end-stage renal disease (ESRD) pediatric patients. Our results are consistent with previous studies demonstrating that even in the current era, renal osteodystrophy is a common and underappreciated cause of morbidity among children with ESRD.

This high prevalence of growth retardation (68.3%) identified in this cohort was consistent with patterns observed in previous reports from comparable populations. Although other factors including mineral dysregulation, metabolic alkalosis/acidosis and malnutrition are contributory to over 60% of the cases of linear growth failure in pediatric dialysis, which were evident in our patient population with hypocalcemia, elevated phosphate and parathyroid hormone level and hypoalbuminemia state. In our subgroup analysis, we observed the growth retarded children at baseline had lower levels of serum calcium and vitamin D, higher levels of phosphorus and iPTH, longer dialysis duration with associated endochondral ossification impairment and delayed skeletal maturation (Imel & Carpenter, 2018).

Highly prevalent musculoskeletal symptoms included bone pain (60.0%) and muscle weakness (48.3%). These results are supported by previous work in this area done by (Hung *et al.*, 2023) that are in line with the neuromuscular complaints of our children with CKD this is a probable result of disturbance in calcium-phosphate metabolism and uremic toxin accumulation. The above symptoms have remarkable implications in orthopedics since chronic pain, decreased physical activity, and the propensity for having a fracture (seen in 15% in our cohort) can significantly reduce functional independence; burdening caregivers; while requiring more orthopedic interventions. The presence of skeletal deformities in >1/3rd of our patients hints at a protracted mineral dysregulation during vulnerable growth times.

The most common radiological abnormality was osteopenia, present in 36.7% followed by subperiosteal bone resorption and Rugger-Jersey spine. These changes confer the distinct spectra of renal osteodystrophy, especially hyper parathyroid bone disease due to uncontrolled secondary hyperparathyroidism. (Rejnmark & Ejlsmark-Svensson, 2020) in pediatric dialysis study, reported similar radiographic studies in which subperiosteal resorption was found along with extremely high PTH levels. This was confirmed by the current results: mean iPTH levels were over 500 pg/mL in patients with and without these abnormalities. In 40% of our patients, even radiologically no clear signs of rickets were visible, which again supports the hypothesis that there might be a stage suffering from biochemical disturbances prior to visually evident bone damage.

From a treatment perspective, the study found significant disparities in the effectiveness of CKD-MBD care strategies. Most patients received calcium-based phosphate binders; however, they had the highest rates of radiological abnormalities (36.8%), echoing recent literature concerns regarding calcium overload and the risks for vascular calcification in paediatric patients (Shroff, 2021). In contrast, the less widely used non-calcium phosphate binders (25%) showed less biochemical and radiological disturbance, supporting findings from randomized trials which call for their greater use in children.

More than two-thirds of the patients were receiving calcitriol therapy, and although PTH control was moderate, this drug was not uniformly effective as evidenced by each patient's fluctuating level, a consequence of its suppressive, not restorative-function. In the same European studies, dietary phosphate restriction alone failed to produce improvements in biochemical targets supporting our findings where CKD-MBD outcomes were sub-optimal with dietary management only and no pharmacologic support (Ayoob & Mahan, 2022). Noteworthy, better dialysis adequacy was a centerpiece to achieve a good management of mineral imbalance and patients with the optimal Kt/V showed lower serum phosphate levels, PTH, and radiographic abnormalities, supporting that optimization for solute clearance is important not only for controlling bone health. The two cases of parathyroidectomy in our cohort, although unusual, were more successful operations and redefine the surgical approach to this problem for the whole region, particularly given that Japanese data shows a similar trend (Pavlidis & Pavlidis, 2023).

Lastly, mineral metabolism showed high relation with pediatric growth as seen in our study comparing children with FTT and normal growing ones. Levels of all key biochemical abnormalities (hypocalcaemia, hyperphosphatemia, high iPTH, low 25(OH)D and elevated ALP) were significantly worse in growth-impaired compared to non-growth-impaired children, thus supporting a multifactorial model for development of ESRD-related growth failure. These findings also support global registry data that growth hormone therapy may not be successful without appropriate control of CKD-MBD (KDOQI Guidelines 2019).

Conclusion

This study aims to shed light on the substantial orthopedic and systemic morbidity of renal osteodystrophy (ROD) in children with end-stage renal disease (ESRD), therefore providing an important evaluation of its clinical, biochemical, radiographic and therapeutic characteristics. The high burden of skeletal complications including bone pain and deformities, growth retardation and fractures thus support the assertion that ROD extends beyond a biochemical disturbance and is an important contributor to morbidity in children with CKD. These results reaffirm our understanding that increased parathyroid hormone, phosphate wasting, and vitamin D-deficiency hypocalcemia are driving forces for skeletal pathophysiology and growth failure. The well-documented association of these markers with clinical and imaging-assessed orthopedic outcomes underscores the importance of comprehensive assessment of bone health in pediatric nephrology. Interestingly, the type of treatment modality had an influence in the outcome; calcium-based phosphate binders and calcitriol were used mostly but non-calcium binders, adequate dialysis showed better biochemical control and radiological outcomes. Strikingly, parathyroidectomy although an uncommon procedure was associated with near-complete and consistent reversal of biochemical derangements as well as skeletal pathology thereby suggesting good utility in resistant cases.

The study also shows that those with prolonged dialysis and ongoing uncorrected metabolic derangements contribute to significant orthopedic risk in the pediatric population. Many of these findings lend support to a transformation in diagnostic and therapeutic paradigms towards early intervention, personalized medical treatment, and multidisciplinary team collaboration across the specialties of nephrology, endocrinology, and orthopedics. Research priorities include harnessing the potential for reversal of bone damage, examining whether additional new exploratory therapies are effective, and high-quality studies to validate non-invasive tools in monitoring bone disease in children. Greater knowledge regarding the metabolic pathogenesis and orthopedic consequences is needed to ultimately improve bone health in children with ESRD, including how best to introduce evidence-based strategies.

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