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Correlation between DKK-1 Level and Bone Density Status in Children on Maintenance Haemodialysis

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Abstract

Background: Renal osteodystrophy (ROD) is a bone disorder resulting from chronic kidney disease (CKD) and related metabolic diseases. Dickkopf-related protein-1 (DKK-1) is critical in regulating bone biology. **This study aimed** to evaluate the serum DKK-1 level as a bone marker in children with CKD who undergo regular hemodialysis (HD). **Subjects and Methods**: This case-control study involved 40 children with CKD on HD and 40 healthy children as controls. The study measured serum DKK-1 levels and performed a dual-energy X-ray absorptiometry scan (DEXA) in line with routine laboratory investigations. **Results:** There was a significant increase in the serum level of DKK-1 in the patient group compared to the control group. The DKK-1 levels were 2540.65 (2215.4 - 2909.2) pg/ml and 1110.45 (885.45 - 1527.65) pg/ml, respectively, with a p-value of less than 0.001. In the hemodialysis group, 25 patients (62.5%) had low bone mineral density (BMD) with a Z-score of under −2.0. Eighteen of these patients had low BMD in both the neck of the femur and lumbar spines. Additionally, there was a significant increase in serum DKK-1 level in patients with low BMD (2567.35 (2303.8 - 3108.1) pg/ml) compared to patients with normal BMD (2454 (1859 - 2820) pg/ml) ($p = 0.041$). There was also a significant positive correlation between DKK1 level and phosphorus, alkaline phosphatase, and Parathormone serum levels. **In conclusion,** the study indicates a clear correlation between DKK-1 and BMD in children undergoing maintenance hemodialysis. DKK1 is a promising biomarker for CKD-MBD.

Keywords

DKK-1, Children, Haemodialysis, Bone Density Status

1. Introduction

Chronic kidney disease, metabolic bone disease (CKD-MBD), is a health condition that affects the kidneys and bones, leading to an increased risk of bone fractures and vascular calcification. Research indicates that the Wnt/β-catenin pathway could play a significant role in treating CKD-MBD. This pathway contributes to bone formation, and studies have shown that CKD patients have increased levels of Wnt inhibitors [1] [2].

The Wnt/β-catenin pathway has been implicated in developing adynamic bone disease in early-stage chronic kidney disease (CKD). Dickkopf-related protein 1 (DKK1) and sclerostin are antagonists of the Wnt/β-catenin pathway yet have not been widely used as clinical indicators of bone disease [3].

Dickkopf-related protein 1 (Dkk-1) is crucial in developing and maintaining healthy bones in both embryonic and adult stages. It is expressed in various body parts, including osteoblasts and osteocytes, as well as the skin and endothelium. Its primary function is to inhibit the canonical Wnt pathway by binding to the Wnt-coreceptor LRP5/6, which is well documented [4].

Bone biopsy remains the gold standard tool for evaluating renal osteodystrophy (ROD), but it is an invasive procedure [5]. Despite a growing interest in the ability of newer bone biomarkers to discriminate between different forms of ROD [6].

Imaging techniques, such as dual-energy X-ray absorptiometry, can help determine bone mineral density and help predict fracture risk in CKD patients. However, they do not distinguish among types of ROD [7].

There have not been many studies that extensively investigated the link between bone density status and Dkk-1 in children who are on maintenance hemodialysis.

This research aims to establish a direct correlation between serum DKK1 levels and bone density in children with CKD.

2. Subjects and Methods

The current case-control study was conducted to determine the relationship between Dickkopf-related protein 1 (Dkk-1) serum levels and bone density in paediatric patients with chronic kidney disease (CKD) undergoing maintenance hemodialysisat least three months prior to the study [8]. The study was conducted between February and August 2022 at Alzahraa Hospital Al-Azhar University, involving 80 participants. The participants were selected from the haemodialysis unit and the outpatient paediatric clinic and were divided into two groups. The dialysis group consisted of 40 patients (13 female, 27 male) with end-stage renal disease who had been undergoing regular haemodialysis for more than three months. The control group consisted of 40 healthy children (19 female, 21 male) of the same age and sex selected from the general paediatric clinic. The study excluded children with chronic or acute infections, other chronic diseases, congenital bone deformities, or recent bone fractures.

Before the study, the parents of the participating children were informed of the study's purpose. They gave written consent to the ethical guidelines of the AL-Zahraa University Hospital's ethical committee, which is affiliated with the Al Azhar University Faculty of Medicine (for Girls) in Cairo, Egypt. All patients underwent the same procedures during the study, which took place at the paediatric nephrology and haemodialysis unit, clinical pathology, and internal medicine departments.

The study involved taking a complete medical history of each participant, including information about the cause of their chronic kidney disease (CKD), the onset and duration of their haemodialysis treatment, any bone pain or recent fractures they may have experienced, and any medications they were taking. Additionally, all study populations underwent routine and specific laboratory and radiological investigations to assess bone density status.

Laboratory investigations

Sampling

Blood samples were drawn in the morning after an overnight fast of at least 12 hours before the start of the mid-week HD session. A total of 5 millilitres of venous blood was collected for analysis. 2 millilitres of blood was utilised for a complete blood count test using EDTA solution. The remaining 3 millilitres of blood were allowed to clot, and the serum was immediately separated to assess biochemical parameters such as Blood Urea Nitrogen (BUN), serum creatinine, calcium, phosphorus, ALP and PTH. The HITACHI auto analyser performed all tests. Additionally, 2 millilitres of the serum sample were carefully labelled and stored at −20˚C until the dickkopf assay was conducted using the ELISA technique.

Dickkopf levels were measured in serum using the ELISA method with Fine Test kits. Samples were added to wells coated with a specific antibody, followed by incubation with biotin-labelled antibodies and HRP conjugate. A TMB substrate was added, creating a blue colour in wells containing Dickkopf. After stopping the reaction with sulphuric acid and reading the optical density at 450 nm, the results were calculated using a standard curve.

https://www.fn-test.com/

Radiological investigations

Dual-energy X-ray absorptiometry:

A dual-energy X-ray absorptiometry test was done in the internal department of Al-Zahra University Hospital using a DEXA device to assess bone mineral density. An experienced technician carried out all BMD measurements. For the test, the patient lay on an examining table in the supine position for imaging of the lumbar spine and femoral neck. The scanner rapidly directs X-ray energy from two sources towards the bone being examined alternatingly at a set frequency.

The examination used a GE Lunar Prodigy DF+16170 DEXA scanner (Norland) with advanced fan-beam technology with the patient lying supine and with

lateral decubitus. The BMD measurement was carried out on the lumbar spine, and all patients generated anteroposterior (AP) images.

The lumbar spine was used to measure the BMD of patients through anteroposterior (AP) images. A diagnosis was made if the Z-score was below −2, indicating a BMD below the expected range for the patient's age. The recommendations were to measure BMD at two sites (hip and spine), use AP images of L1 - L4 for spine BMD measurement, use the proximal neck of the left femur for hip BMD measurement, calculate BMD in grams per square centimetre using a scanner, and consult a reference database for values and curves. BMD was measured on the lumbar spine in all patients, and the AP images were generated. A Z-score < −2, which was below the expected range for age, was indicative of the diagnosis. The recommendations included measuring BMD at two sites, using specific AP images for measurement, using a scanner to calculate BMD, and consulting a reference database for values and curves [9].

Statistical analysis

The data was collected, revised, coded, and entered into the Statistical Package for Social Science version 21 (IBM *et al.*, USA). The correlation between two studied parameters within the same group was evaluated using Spearman correlation coefficients. The Receiver Operating Characteristic (ROC) curve was used to determine the best cutoff point with sensitivity and specificity. Probability values were interpreted as follows: $p > 0.05$ was considered non-significant, and $p < 0.05$ was significant.

3. Results

Table 1 shows that the patients had considerably higher blood pressure and a decreased Hb level, Hct%, platelet count, TLC, and calcium level compared to the control group. Additionally, the patient group showed a significant increase in pH, ALP, PTH, urea, and creatinine levels. Finally, there was a substantial decrease in the Lumber spine and neck of Femur Z-score in the patients' group compared to their controls. Furthermore, the serum DKK1 level in children undergoing haemodialysis was notably higher than their controls.

Table 2 indicates that when comparing patients with average and low bone mineral density (BMD) based on traditional markers of BMD and DKK1, there was a significant increase in DKK1 levels in patients with low BMD compared to those with normal BMD. However, the two groups had no significant difference in traditional markers.

Table 3 displays that DKK1 has a noteworthy positive correlation with age, systolic blood pressure (SBP), diastolic blood pressure (DBP), urea, creatinine, calcium, pH, alkaline phosphatase (ALP), and parathyroid hormone (PTH). Conversely, there is a noteworthy negative correlation between DKK1 and weight, height, total leukocyte count, red blood cells, haemoglobin, hematocrit percentage, and platelets. Furthermore, there is a significant negative correlation between DKK1 and the Z-score of the lumbar spines and neck of the femur.

Table 1. Comparison between the patients' group and control group regarding laboratory parameters and DEXA findings of lumber spine and neck of femur.

Variable	Control group	Patients group	Test value	p-Value
	No. = 40 Mean± SD	No. = 40 Mean ± SD		
Age (years)	10.40 ± 2.80	11.98 ± 3.39	2.268•	0.026
SBP (mmHg)	101.75 ± 7.89	131.0 ± 13.92	−11.560•	0.000
DBP (mmHg)	61.38 ± 6.20	83.63 ± 9.13	−12.753•	0.000
TLCX 10^3/UL	7.72 ± 1.30	6.61 ± 2.31	2.655•	0.010
RBCsX 10^6/UL	4.74 ± 0.37	3.51 ± 0.63	10.669•	0.001
Hb (gm/dl)	12.00 ± 0.86	9.46 ± 1.85	7.911•	0.000
Hct%	36.46 ± 2.50	28.61 ± 5.75	7.922•	0.000
Platelet 10^3 /UL	291.78 ± 54.88	224.65 ± 79.96	4.377•	0.000
Ca (mg/dl)	9.08 ± 0.37	8.46 ± 2.55	1.543•	0.127
Ph (mg/dl)	4.36 ± 0.30	5.44 ± 2.18	−3.100•	0.003
ALP (U/l)	174.5 (154 - 212)	316 (176.5 - 494.5)	−3.864≠	0.001
PTH (pg/ml)	54.5 (44.5 - 63.0)	342.5 (173.5 - 714)	−7.430≠	0.001
Urea (mg/dl)	11 (6.5 - 15)	32.5 (24.5 - 48.5)	−7.249≠	0.000
Creatinine (mg/dl)	0.4 (0.25 - 0.50)	2.1 (1.65 - 3.20)	−7.704≠	0.000
DKK1 (pg/ml)	1110.45 (885.45 - 1527.65)	2540.65 (2215.4 - 2909.2)	−6.851	0.001
Lumber spines Z-score	0.75 (0.13 - 1.0)	−1.4 (−2.45 - −0.45)	−6.037≠	0.001
Neck of femur Z-score	0.72 (−0.49 - 1.20)	−1.15 (−1.85 - −0.10)	−4.841≠	0.001

Table 2. Comparison between patients with average and low bone mineral density regarding traditional bone markers and DKK1 serum levels.

Variable	DEXA scan		Test value	p-Value
	Normal bone density	Low bone density		
	No. = 22	No. = 18		
Ca (mg/dl)	9.03 ± 2.71	7.75 ± 2.20	1.617•	0.114
Ph (mg/dl)	5.80 ± 1.91	4.99 ± 2.45	1.163•	0.252
ALP (U/L)	275.5 (170 - 474)	336.5 (190 - 515)	−1.292≠	0.196
PTH (pg/ml)	228.5 (161 - 477)	434 (214 - 923)	−0.462≠	0.644
DKK1 (pg/ml)	2286.43 ± 586.99	2781.85 ± 683.46	−2.467•	0.018

Table 3. The correlation between DKK1 levels in patients' group with clinical and laboratory data.

Variable	DKK1	
	r	p-Value
Age	0.241*	0.032
Sex	−1.632	0.103
Wt. (kg)	−0.225*	0.045
Ht (cm)	−0.254*	0.023
BMI	−0.038	0.741
SBP (mmHg)	0.675**	0.001
DBP (mmHg)	0.680**	0.001
TLCX 10^3/UL	−0.318**	0.004
RBC 10^6/UL	−0.582**	0.001
Hb (gm/dl)	−0.403**	0.001
Hct%	−0.491**	0.001
PlateletX 10^3/UL	−0.256*	0.022
Urea (mg/dl)	0.705**	0.001
Creatinine (mg/dl)	0.659**	0.001
Ca (mg/dl)	0.014	0.904
Ph (mg/dl)	0.252*	0.024
Alk. phosphatase (U/l)	0.321**	0.004
PTH (pg/ml)	0.662**	0.001
Lumber spines Z-score	−0.539**	0.001
Neck of femur Z-score	−0.406**	0.001

Table 4, Figure 1, and Figure 2 indicate that a DKK1 serum level of over 1851 pg/mL is the ideal threshold for predicting CKD-MBD in children on maintenance hemodialysis. This prediction has a sensitivity of 87.5% and a specificity of 97.5%. Moreover, CKD-MBD can be accurately predicted if the lumbar spine Z-score is less than or equal to 0.2, with a sensitivity of 92.5% and specificity of 75.0%, and if the neck of the femur Z-score is less than or equal to 0.3, with a sensitivity of 87.5% and specificity of 72.5%.

Figure 3 According to the study results, patients had an average bone density of 15 (37.5%). However, children had a higher prevalence of low bone mineral density in the neck of the femur and lumbar spine, with 18 (45.0%) affected. Only 4 (10.0%) children had low BMD in the lumbar spine, and 3 (7.5%) had low BMD in the neck of the femur.

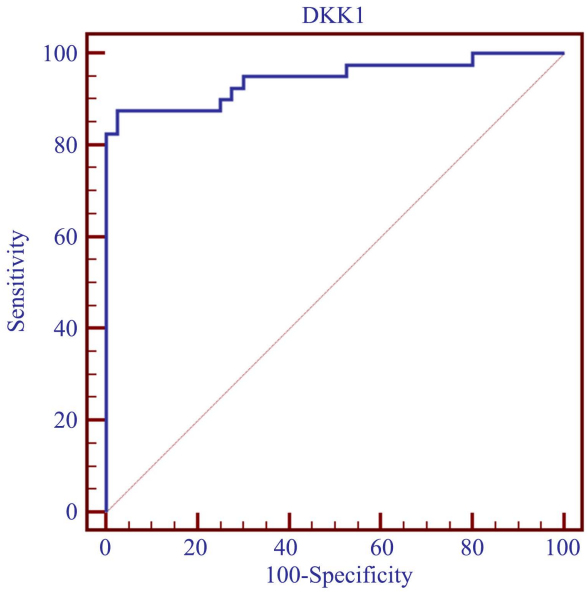

Figure 1. The ROC curve for DKK-1 predicts CKD-MBD in hemodialysis children.

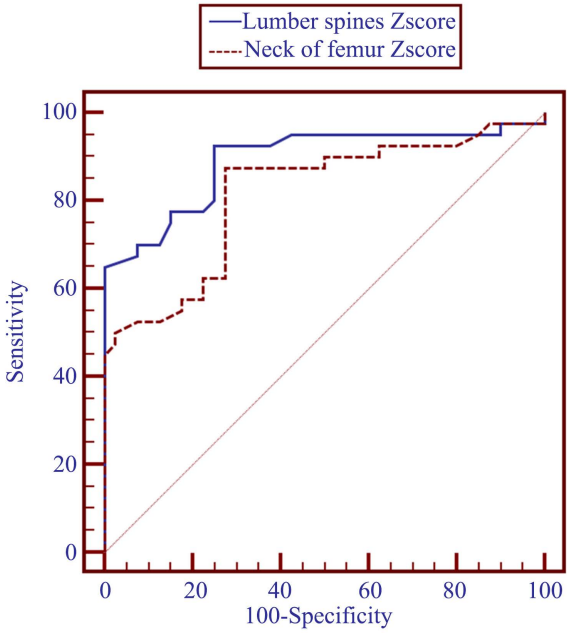

Figure 2. Receiver operating characteristic curve (ROC) for Lumber spines and neck of femur DEXA parameters in predicting (CKD-MBD) in hemodialysis children.

Table 4. Cut-off point, sensitivity, and specificity of DKK-1 serum level and DEXA parameter in predicting (CKD-MBD) in hemodialysis children.

Cut off point	AUC	Sensitivity	Specificity	+PV	−PV
DKK-1 > 1851 (pg/ml)	0.945	87.50	97.50	97.2	88.6
Z-score for lumber spines ≤ 0.2	0.892	92.50	75.00	78.7	90.9
Z-score for the neck of the femur ≤ 0.3	0.814	87.50	72.50	76.1	85.3

Figure 4 and Figure 5 According to their findings, the lumbar spine Z-scores of the dialysis group were significantly lower than those of the control group. One of the dialysis group's lumbar spine Z-scores was −2.8, while the control group's Z-score was 1.8.

Figure 6 and Figure 7 revealed significantly lower bone mineral density (BMD) Z-score in the femur neck of one dialysis patient (−2.6) compared to the control (0.8).

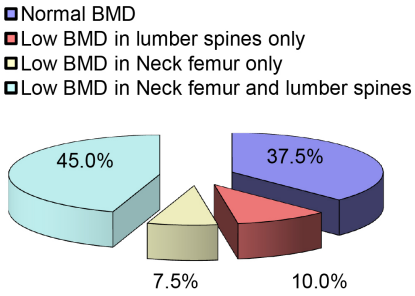

Figure 3. The distribution of DEXA findings in the hemodialysis group.

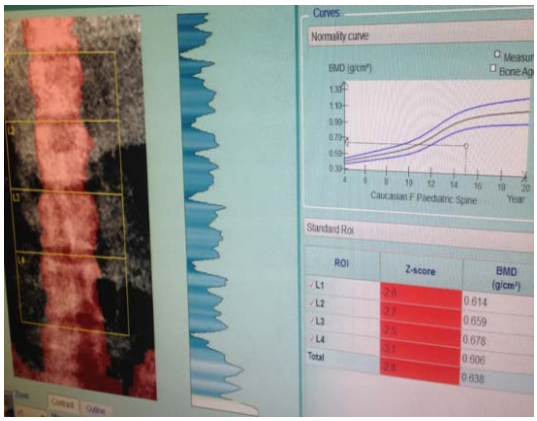

Figure 4. BMD in lumber spines with Z-score (−2.8) (one of the dialysis group).

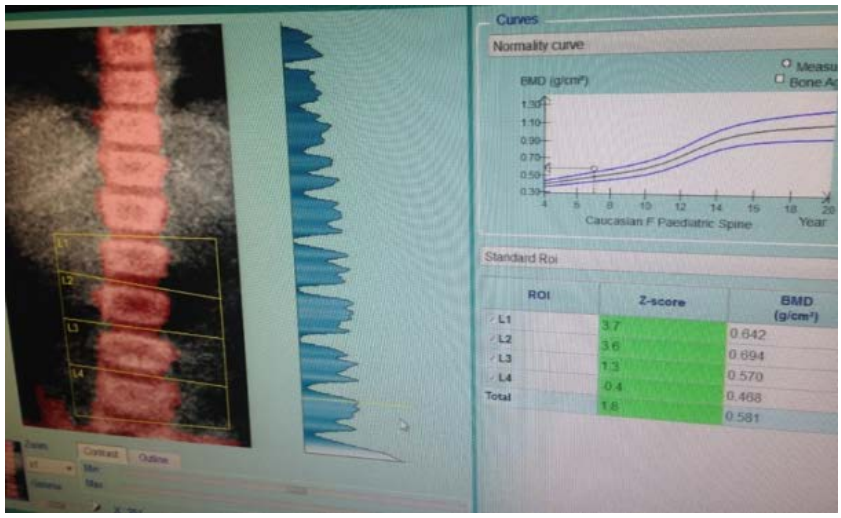

Figure 5. BMD in the lumbar spine with a Z-score of 1.8 (one of the control groups).

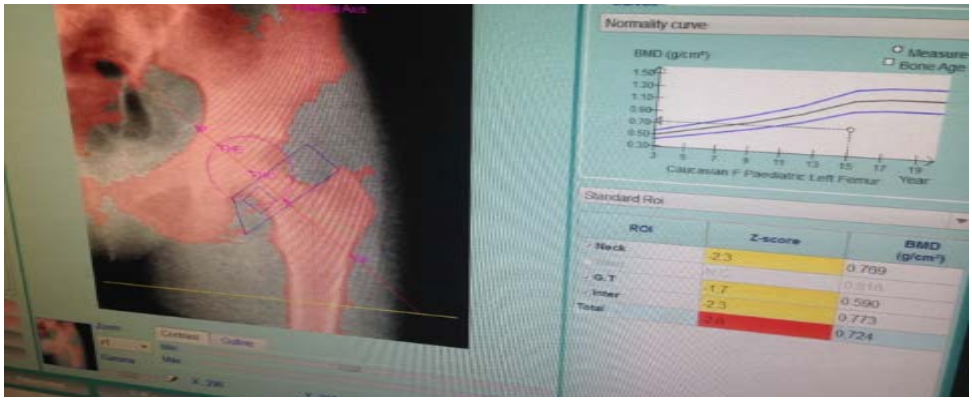

Figure 6. BMD in the femur neck with a Z-score of −2.6 (one of the dialysis group).

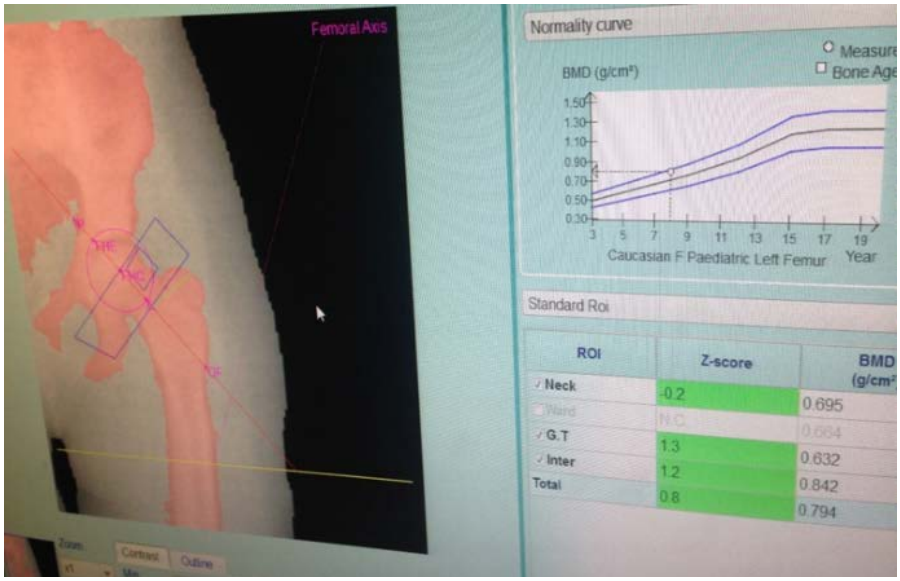

Figure 7. BMD in the femur neck with a Z-score of 0.8 (one of the control group).

4. Discussion

Renal osteodystrophy is a severe complication of end-stage renal disease, causing skeletal and extra-skeletal problems. Osteodystrophy cannot be entirely prevented in hemodialysis patients. However, timely and appropriate interventions can help reduce associated symptoms and comorbidities. To better understand the pathophysiology of renal osteodystrophy, it is crucial to comprehend the factors contributing to ongoing bone remodeling [7]. This research aims to assess the potential of DKK1 as a contributing factor and early diagnostic marker for CKD MBD. In healthy bone maintenance, mature osteoblasts release DKK1, which inhibits the Wnt signaling of osteoblast precursors [10].

Our research has revealed that children undergoing hemodialysis have considerably higher levels of DKK1 than healthy children. Additionally, those children with low bone density exhibit a more significant increase in DKK1 levels. Elevated levels of DKK1 serum level have been linked with osteolytic bone lesions. DKK1 reduces the functionality of osteoblasts while encouraging osteoc-

last maturation, as reported by [11] [12] [13], also demonstrated a noticeable rise in dickkof-1 serum levels among CKD patients. DKK1 expression is typically high during development but low in most adult tissues. However, Overexpression of DKK1 has been linked with several diseases. Additionally, elevated levels of DKK1 in peripheral blood are associated with chronic inflammatory disorders [14].

Our study has shown a significant correlation between patient age and serum DKK-1 levels. This finding is consistent with a previous case-control study by [15], which also found a strong correlation between DKK1 serum levels and age.

The study showed a positive connection between serum DKK1 and the build-dup of uremic toxins, urea, and creatinine in haemodialysis patients. This build-up leads to a decline in Wnt/β-catenin signalling in osteoblasts, which increases the expression of Wnt signalling inhibitors like DKK-1. [16] and [17] have also reported similar findings.

Moreover, the current study found a significant relationship between DKK1 and the traditional bone turnover markers, including serum phosphate and PTH. Hou *et al.*'s study discovered that DKK1 levels were significantly linked to markers of bone turnover, like serum phosphate and PTH.

Rossini et al. (2015) [15] conducted a case-control study that revealed a correlation between serum levels of DKK1 and PTH. However, [18] found no significant correlation between serum DKK1 levels and calcium, phosphate, and PTH levels in patients with chronic kidney disease undergoing haemodialysis.

The current study has found an interesting positive correlation between serum DKK-1 and SBP/DBP. Available data suggest that Wnt/β-catenin pathway inhibitors, sclerostin and Dkk-1, could participate in the pathogenesis of extra skeletal calcification with a potential impact on arteriosclerotic vascular damage and valvular calcification [19] [20] [21]. According to research by **[22]**, the Wnt signalling pathway may be involved in vascular calcification (VC) based on animal studies. The study also found a direct correlation between serum DKK1 levels and weight/BMI in haemodialysis patients. This supports the findings of [23], who reported a positive correlation between serum DKK1 and BMI in humans. Therefore, DKK1 could be used as a biomarker for adiposity.

In 2021, an exciting study by [24] provided experimental evidence for a vessel-bone axis. This was documented by the transplantation of aortic tissue from uremic rats into rats with normal kidney function.

The current study conducted DEXA scans and found that 62.5% of children undergoing haemodialysis had low bone mineral density (BMD). Low BMD may occur due to high turnovers associated with hyperparathyroidism and hyperphosphatemia [25] [26], as observed in the haemodialysis group of the current study, or due to low turnovers accompanied by lower levels of Parathyroid Hormone (PTH), which is often typical [27]. ROD initiates when the renal function starts to deteriorate. The prevalence rate of ROD in developing countries ranges from 33.3% in Egypt to 81% in Brazil [28].

The results of this study are in line with those of [29], who also noted that a significant number of chronic kidney disease (CKD) patients have low bone mineral density (BMD). [30] reported that chronic hypocalcaemia or hyperphosphatemia, prevalent in children undergoing frequent haemodialysis (HD), can lead to impaired bone mineralisation. The study also revealed a significant negative correlation between DKK1 serum levels and BMD in the study's patient population. This supports our findings that DKK1 inhibits the Wnt pathway and plays a role in bone turnover, as [31] proposed.

The study revealed that patients with low Bone Mineral Density (BMD) have high levels of DKK-1 in their blood. This happens because DKK-1 attaches to LRP5/6 receptors and blocks the Wnt signalling pathway, which results in reduced bone formation. The Wnt/β-catenin signalling pathway controls osteogenesis and bone formation, as noted by [32].

Our findings are supported by [15], who reported that DKK1 serum level was inversely related to lumbar spine Z-score BMD., a significant negative correlation between DKK1 and total hip BMD Z-score.

Based on the analysis of the ROC curve, it was determined that the optimal cut-off point for DKK1 in predicting CKD-MBD is more significant than 1851 pg/mL. This cut-off point has a sensitivity of 87.50% and a specificity of 97.50%.

In addition, the DEXA ROC curve showed that the best cut-off point for femur neck BMD is less than or equal to 0.3, with sensitivity and specificity of 87.50% and 72.50%, respectively. The best cut-off point for lumber spines BMD is less than or equal to 0.2, with sensitivity and specificity of 92.50% and 75%, respectively, in predicting CKD-MBD.

5. Conclusion

In conclusion, DKK1 is a highly sensitive and specific predictor of CKD MBD, significantly correlating to the BMD. Inhibition of Dickkopf-1 presents a promising strategy for preserving bone mass in children on regular hemodialysis.

Study Limitation

There is no available data on the relationship between DKK1 and CKD MBD in pediatric patients on maintenance hemodialysis. This study is the first to evaluate the correlation between DKK1 and DEXA findings in those patients.

Conflicts of Interest

The authors have no conflict of interest to declare.

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