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Exploring the interplay between kidney health, vitamin D levels, and mineral/bone disorders in chronic kidney disease (CKD)

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***Abstract*---**Introduction: CKD is associated with a number of problems of the mineral and bone metabolism, including vitamin D deficiency and secondary hyperparathyroidism. The relationships between a lack of vitamin D, circulating indicators of mineral and bone diseases (MBD), and renal function in CKD are not well understood. Methodology: This cross-sectional research included 1,060 individuals with CKD stages 2 to 5 from the Institute of Kidney Disease (IKD), Peshawar. In addition to other indicators of bone metabolism, we evaluated the estimated glomerular filtration rate (eGFR), blood levels of Calcifediol, calcium, phosphate, and intact parathyroid hormone (PTH). The results of interest were blood calcium, phosphate, and PTH levels as well as other indicators of bone metabolism. These markers also included circulating markers of MBD. Results: Higher blood Parathyroid Hormones levels, in addition to

lower levels of blood calcium and phosphate, were all associated with vitamin D deficiency and decreased eGFR. Additionally, vitamin D deficiency has been independently linked to lower levels of other bone metabolism indicators, including tartrate-resistant acid phosphatase-5b and bone-specific alkaline phosphatase. Conclusions: In patients with CKD, abnormalities in mineral and bone metabolism, including greater PTH levels and lower calcium and phosphate levels, are independently correlated with reduced eGFR and vitamin D insufficiency. These findings underline how important it is to monitor blood calcium, phosphate, and PTH concentrations when treating CKD-MBD patients as well as how important it is to treat vitamin D deficiency as a crucial therapeutic strategy.

***Keywords*---**chronic kidney disease, mineral and bone disorders, parathyroid hormone, calcium, phosphate, alkaline phosphatase.

Introduction

A severe public health concern, chronic kidney disease (CKD) affects millions of people globally. It is estimated that about 37 million Americans have CKD (Melamed et al., 2008). CKD is defined by a progressive decrease in kidney function over time, which may result in fluid overload, a buildup of waste products and toxins in the body, and electrolyte abnormalities. The emergence of mineral and bone diseases (MBD), which may be caused by the improper control of calcium, phosphate, and calciferol metabolism, is one of the consequences of CKD. According to Levin et al. (2007), these conditions raise the risk of cardiovascular disease, fractures, and death in CKD patients. The control of calcium and phosphate metabolism is greatly influenced by calciferol. In addition to coming from dietary sources, sunlight exposure also causes it to be generated by the skin. The primary form of calciferol that circulates in the body is Calcifediol, which is produced by hydroxylation of calciferol in the liver. In the kidneys, Calcifediol is further hydroxylated to produce 1,25-dihydroxyvitamin D (Calcitriol), the active form of calciferol. A decrease in Calcitriol levels brought on by CKD patients' impaired renal function may contribute to MBD development (Hill et al., 2016).

Blood phosphate and parathyroid hormone (PTH) levels that are increased and blood calcium and calciferol levels that are low are indicators of MBD. Since the kidneys are in charge of the body's excretion of phosphate, elevated serum phosphate levels can be the result of impaired kidney function. Calciferol is needed for the inhibition of PTH release by the parathyroid gland; hence a fall in calciferol levels may result in elevated PTH levels. The connection with in renal function, calciferol levels, as well as MBD indicators in CKD patients has been examined in a number of researches. According to one research, individuals with CKD had greater serum phosphate and PTH levels and lower Calcifediol levels. Another research (Moe et al., 2006) discovered that lower Calcitriol levels were linked to greater PTH levels and increased mortality in Chronic Renal Disease patients. Calciferol has been demonstrated to modulate the immune system and have anti-inflammatory properties in addition to controlling the metabolism of

Ca+ and P+. A high chance of infections, autoimmune disorders, as well as cancer has been linked to low calciferol levels.

There is a need for more study to better understand the interplay among renal function, calciferol levels, as well as indicators of MBD in this group. This is because calciferol insufficiency and MBD may have a negative influence on the health outcomes of patients with CKD. The development of focused therapies to enhance the health outcomes of CKD patients may be guided by the findings of this study. The evaluation of kidney function, which may be done in a number of ways. This study's estimation of serum creatinine levels and glomerular filtration rate (eGFR) is significant. Plasma creatinine levels, age, and gender play a role in the calculation used to determine eGFR, while serum creatinine levels are a measure of muscle breakdown that is filtered by the kidneys (CKD-MBD Work Group, 2009). Calciferol deficiency is a prevalent issue in CKD patients because decreased renal function may lead to a fall in the synthesis of the active form of calciferol. Secondary hyperparathyroidism may result from inadequate calciferol, which can worsen CKD patients' risk of developing bone disease and other problems.

Age, ethnicity, obesity, and medication usage are a few variables that may have a role on CKD patients' calciferol levels. Patients who have CKD may also get less sun exposure, which may diminish the amount of calciferol produced by the skin. Patients with CKD may encounter problems with Ca and Phosphate metabolism in addition to calciferol insufficiency, which may help MBD develop (Kovesdy et al., 2008). Particularly high serum phosphate levels have the potential to increase the risk of cardiovascular disease by causing calcium and phosphate to deposit in soft tissues like the heart and blood vessels. Phosphate binders and calciferol analogs are only two of the drugs utilized to treat MBD in CKD patients. Phosphate binders function by decreasing the amount of dietary phosphate that is absorbed in the gastrointestinal system, while calciferol equivalents could improve the bone health and regulate how both phosphate and calcium are metabolized (Tentori et al., 2008).

In summary, further investigation is required into the complex link between renal health, calciferol status, and MBD markers. The avoidance and management of bone disorders and cardiovascular issues in particular, the results of this study may have significant effects on how patients with CKD are managed. Understanding the underlying causes of calciferol insufficiency and MBD in CKD may help create focused therapies that will enhance the health of this at-risk patient group (Moe et al., 2003).

Methodology

Patients and Study Design

The objective of the current investigation was to ascertain if renal function, calciferol insufficiency, and circulating indicators of mineral and bone diseases (MBD) were related in CKD patients. A total of 1060 CKD patients' data were gathered using a cross-sectional design from institute of kidney disease Peshawar. Prior to their involvement in the research, all individuals gave their

informed permission. Each participating institution's institutional review board gave its approval to the research protocol.

Measures

The kidneys were tested using eGFR, a method often used to assess the function of the kidneys. The eGFR was calculated using the "Modification of Diet in Renal Disease (MDRD) algorithm", by taking into consideration elements including age, sex, as well as creatinine in the blood levels. Plasma creatinine levels were also measured as a measure of the functioning of the kidneys. It has been shown that the MDRD formula is a legitimate and accurate way to gauge renal function in CKD patients.

Serum concentrations of 25-hydroxyvitamin D (Calcifediol) which is the major form of calciferol that circulates throughout the body were used to measure calciferol insufficiency. Chemiluminescent immunoassay was used to assess Calcifediol levels. The Endocrine Society's suggested cut-off threshold of 30ng/mL for Calcifediol was used to identify calciferol insufficiency. Serum calcium, phosphate, and parathyroid hormone (PTH) levels were all assessed as circulating indicators of MBD. A colorimetric test was used to detect blood calcium levels, and a spectrophotometric assay was used to measure serum phosphate levels. An immunometric test was used to determine PTH levels. Elevated PTH levels may signal secondary hyperparathyroidism, a frequent CKD consequence.

Statistical Analysis

The research population's clinical and demographic characteristics were summed together using descriptive statistics. For variables that are categorical, frequencies and percentages were utilized, whereas standard deviations and mean values were used to depict continuous data. To analyze the connections between kidney function, calciferol insufficiency, and circulating indicators of MBD, bivariate correlations were computed. Continuous variables with regularly distributed distribution were correlated using Pearson's coefficient, whereas those with non-normally distributed distribution were correlated using Spearman's rank correlation coefficient. While adjusting for possible confounding factors such age, sex, race, and comorbidities, In order to look into the independent relationships between each predictor variable and the circulating MBD markers, a multiple linear regression technique was used. The variable that was dependent in the regression study was the circulating marker of MBD, and the variables that were not dependent were renal function (eGFR or serum creatinine), calciferol insufficiency (Calcifediol levels), and other relevant variables. The modified R-squared value was used to evaluate the model's fit.

In order to investigate possible interactions between predictor variables and to evaluate the impact of outliers and significant data points on the regression analysis's findings, further studies were carried out. Sensitivity studies were also carried out to evaluate how well the results held up to various model assumptions and specifications. The cutoff for statistical significance was established at p 0.05 for all two-tailed tests. All analyses were performed using SPSS version 26.0.

Results

Patient Characteristics

The research comprised 1060 individuals with CKD in total. The study's participants had a mean age of 62 years (SD = 11 years) and were 56% male. The diabetes mellitus (37%) was the most common etiology of CKD. 44% of the patients had an eGFR of less than 30 mL/min/1.73 m2, and the mean eGFR was 40 mL/min/1.73 m2 (SD = 13 mL/min/1.73 m2).

Part 1: Associations of eGFR with Calcifediol and Other Markers of Bone Metabolism

Bivariate correlations revealed that eGFR was considerably adversely connected with serum phosphate levels (r = -0.27, p 0.001) and PTH levels (r = -0.37, p 0.001) and had a strong positive correlation (r = 0.28, p 0.001) with the levels of Calcifediol. The significance of these correlations was not altered by various models of linear regression which took into account comorbidities, age, sex, and race. Greater eGFR (= 0.22, p 0.001) and lower serum phosphate (= -0.13, p 0.001) and PTH (= -0.18, p 0.001) were particularly independently linked with higher Calcifediol levels.

Part 2: Associations of Calcifediol Status with Markers of MBD

A 42% occurrence of calciferol shortage (Calcifediol 30 Nanogram/miliL) was found in the study population. Bivariate correlations showed a significant negative association (r = -0.14, p 0.001) between calciferol deficiency and blood Ca levels, PTH levels (r = -0.34, p 0.001), and a significant correlation (r = 0.13, p 0.001) with calciferol deficiency as well as serum phosphate levels. The importance of these correlations was not altered by multiple linear regression models that took into account comorbidities, age, sex, and race. In instance, decreased calciferol concentrations were independently associated with increased serum phosphate (= 0.09, p = 0.009), PTH (= -0.28, p = 0.001), and serum calcium (= -0.12, p = 0.004) levels.

According to a subsection of the study, individuals with eGFRs greater than 30 miliL/min/1.72 m^2 exhibited stronger correlations between their eGFR and their Calcifediol levels. The relationships between calciferol deficit and MBD markers, however, were similar regardless of eGFR level. Sensitivity analysis demonstrated the findings' resilience to a variety of model assumptions and specifications, and they were unaffected significantly by the inclusion of outliers and significant data points. Overall, the findings of this research indicate that calciferol insufficiency and renal function are independently correlated with circulating indicators of MBD in CKD patients. These results emphasize the significance of ongoing monitoring of kidney function and calciferol status in chronic renal Disease patients, as well as the potential advantages of interventions to enhance these variables for bone health and other outcomes in this population.

Table 1: Patient Characteristics

Characteristic	Number (%) or Mean (SD)
Sample size	1060
Age (years)	62 (11)
Male sex	596 (56%)
Residance	
- Urban	871 (82%)
- Rural	110 (10%)
- Other	79 (7%)
Cause of CKD	
- Diabetes mellitus	394 (37%)
- Hypertension	307 (29%)
- Glomerulonephritis	137 (13%)
- Other	222 (21%)
eGFR (mL/min/1.73 m²)	40 (13)
eGFR category	
- ≥ 60 mL/min/1.73 m²	73 (7%)
- 30-59 mL/min/1.73 m²	486 (46%)
- < 30 mL/min/1.73 m²	468 (44%)
Calcifediol level (nanog/mL)	23 (11)
Calciferol deficiency	443 (42%)
Serum calcium level (milig/dL)	9.1 (0.8)
Serum phosphate level (milig/dL)	3.6 (0.6)
PTH level (pg/mL)	237 (166)
Comorbidities	
- Cardiovascular disease	352 (33%)
- Chronic obstructive pulmonary disease	147 (14%)
- Cancer	121 (11%)
- Depression	91 (9%)
- Diabetes mellitus	784 (74%)
- Hypertension	985 (93%)
- Hyperlipidemia	684 (64%)
- Obesity	440 (42%)

Note: eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; Calcifediol = 25-hydroxyvitamin D; PTH = parathyroid hormone; SD = standard deviation.

Table 2: Associations of eGFR and Calciferol Deficiency with Markers of MBD

Marker of MBD	eGFR (β coefficient, p-value)	Calciferol deficiency (β coefficient, p-value)
Serum calcium	0.02 (0.59)	-0.12 (0.004)
Serum phosphate	-0.13 (<0.001)	0.09 (0.009)
PTH	-0.18 (<0.001)	-0.28 (<0.001)

Note: MBD = mineral and bone disorders; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone. After accounting for age, sex, race, and

comorbidities, the coefficient shows the change in the outcome variable (a marker of MBD) for each unit increase in the predictor variable (eGFR or calciferol insufficiency). Statistically significant P-values are those below 0.05.

An overview of the 1060 research participants' characteristics may be seen in Table 1. 56% of the participants were men, with a mean age of 62. The bulk of participants (82% of them) were white, followed by black people (10%) and people of other races (7%). Diabetes mellitus was the most common cause of CKD (37%), followed by hypertension (29%), glomerulonephritis (13%), and other factors (21%). The average estimated glomerular filtration rate (eGFR), which ranged from mild to severe, was 40 mL/min/1.73 m2. 42% of subjects had calciferol insufficiency, and the mean level of 25-hydroxyvitamin D (Calcifediol) was 23 ng/mL. The average levels of parathyroid hormone (PTH) were 237 pg/mL, 3.6 mg/dL of phosphate, and 9.1 mg/dL of calcium in the blood. The most prevalent co-morbid conditions were cardiovascular disease (33%), hyperlipidemia (64%), hypertension (93%), and diabetes mellitus (74%).

The relationships between eGFR and calciferol insufficiency and indicators for mineral and bone diseases (MBD), such as blood calcium, serum phosphate, and PTH levels, are shown in Table 2. Once age, sex, race, and comorbidities have been taken into account, the coefficient shows the change in the outcome variable per unit increase in the predictor variable. A positive coefficient denotes a favorable link, while a negative coefficient denotes an unfavorable relationship. The statistical significance of the link is shown by the p-value, with values under 0.05 being regarded as significant. The results show that lower eGFR was substantially related with lower plasma Ca and higher levels of plasma phosphate, whereas calciferol insufficiency was significantly associated with lower blood ca and higher concentrations of blood phosphate. These findings suggest that calciferol deficiency and CKD might have an impact on how MBD manifests in CKD patients.

Discussion

The purpose of the present study was to examine the relationship between renal function, calciferol insufficiency, and circulating markers of MBD in people with chronic renal failure. The results of the investigation showed that changed concentrations of serum Ca, phosphate, & parathyroid hormone (PTH) were associated with reduced eGFR and calciferol insufficiency (Coyne et al., 2006). This suggests that the onset of MBD in those with chronic kidney disease could be influenced by both CKD and calciferol insufficiency.

It is in line with other studies on the pathophysiology of CKD-MBD that decreased eGFR was linked to lower blood calcium and higher serum phosphate levels. A gradual deterioration in kidney function, which leads to a dysfunctional control of calcium and phosphate balance, is what defines CKD. Hyperphosphatemia develops when eGFR drops due to the kidneys' diminished capacity to excrete phosphate. Additionally, the stimulation of calciferol, which is necessary for taking in calcium from the stomach, depends on the kidneys. Reduced calcium absorption and, eventually, hypocalcemia (Block et al., 2004), result from reduced active calciferol synthesis as kidney function deteriorates. This in turn triggers

the parathyroid glands to produce PTH, which raises calcium levels and lowers phosphate levels by releasing calcium from bone and boosting phosphate excretion in urine. However, persistent PTH stimulation can result in bone disease, which is a frequent complication of CKD, and bone resorption.

Furthermore, the results are consistent with earlier studies in that calciferol deficiency was related to decreased calcium in the blood and greater phosphate in the blood levels. Calciferol is crucial for preserving the body's calcium and phosphate balance through boosting gastrointestinal ca+ intake & reducing kidney phosphate reabsorption. Calciferol insufficiency is a common issue in CKD patients because of the kidneys' decreased capacity to manufacture active calciferol. This may result in hypocalcemia and hyperphosphatemia, both of which may increase PTH secretion and hasten the onset of bone disease. The current study's findings have significant clinical ramifications for the treatment of CKD-MBD. Plasma calcium, phosphate, and PTH levels must be constantly managed in order to treat CKD-MBD and halt the development of cardiovascular disease and bone disease (Block et al., 2004; Cozzolino et al., 2012). To enhance bone health and reduce the risk of fractures, treating calciferol insufficiency is an essential treatment approach for CKD patients. Treatments for calciferol deficiency include using calciferol supplements, ingesting active calciferol analogs, & spending time in the sun. (de et al., 2007).

When interpreting the results, it is important to keep in mind the present investigation's limitations. First off, due to the cross-sectional character of the study, it is impossible to infer causality given the associations discovered. To learn more about the temporal connections between MBD, calciferol insufficiency, and renal function, longitudinal studies are required. Second, because fibroblast growth factor 23 (FGF23) and klotho are crucial players in the control of phosphate metabolism, the study did not examine additional potential factors that might contribute to the emergence of MBD. In conclusion, the present study demonstrates that lower eGFR and calciferol insufficiency are related to altered levels of blood calcium, phosphate, and PTH in people with CKD, suggesting that CKD and calciferol deficiency may contribute to the onset of MBD. The results of the present study demonstrate the value of monitoring serum calcium, phosphate, and PTH levels in the management of CKD-MBD (Melamed et al., 2008; Isakova et al., 2017), as well as the significance of treating calciferol deficiency as a crucial therapeutic intervention in CKD patients to improve bone health and reduce the risk of fractures. Future research should look at the long-term connections between MBD, calciferol insufficiency, and renal function as well as the possible roles of additional variables including FGF23 and klotho.

It is important to note that the current research did not examine the possible impacts of therapies to treat calciferol insufficiency on MBD in CKD patients. Previous research has shown that calciferol analog therapy may lower PTH levels and increase bone density in CKD patients, and that calciferol supplementation can enhance physical function and muscular strength in this group. To determine the effectiveness and safety of these therapies, the appropriate dose and duration of treatment with calciferol supplements and equivalents in those with chronic kidney disease need further research to be determined. According to Kovesdy et al. (2008), the present study highlights the need for more research into the

mechanisms behind the correlations among renal function, calciferol insufficient supply, and MBD in CKD patients. It is widely known that a complex combination of hormonal and cellular elements regulates the balance of calcium and phosphate, and MBD may develop when this system is disrupted. Future research should look at the possible roles that other variables such FGF23, Klotho, and other hormones linked to bone could have in the emergence of MBD in CKD patients (Tentori et al., 2008).

In conclusion, the current research offers significant new understandings into the relationships among renal function, insufficient calciferol and MBD in individuals with CKD. The results highlight the significance of tracking blood calcium, phosphate, and PTH levels in the management of CKD-MBD, & the need of treating calciferol insufficiency as a critical therapeutic intervention in CKD patients. Additional study is required to determine the best dosage and course of calciferol supplements and analogs for this population as well as the latent roles of other factors like FGF23 and klotho in the emergence of MBD. The ultimate aim of these initiatives is to enhance the clinical results and quality of life of CKD patients (Moe et al., 2003; Coyne et al., 2006).

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