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The role of fibroblast growth factor 23 in the assessment of complications in chronic kidney disease

Abstract

Secondary hyperparathyroidism is an early-stage complication of CKD (Chronic Kidney Disease). It is associated with disorders in bone metabolism, calcium deposition in vessels and organs, significantly increased risk of cardiovascular disease, and death. In recent years,an increasingly important role has been attributed to fibroblast growth factor (FGF 23) in regulating calcium/phosphate homeostasis, hyperparathyroidism, and its relation to vascularcalcification, and left ventricular hypertrophy.

This study conducted with 110 patients with varying degrees of renal insufficiency shows anincrease in FGF23 and PTH when there is a decrease in glomerular filtration, a direct dependency between the levels of phosphate and PTH and FGF23, and a lack of such between calcium and PTH and FGF23.

Of particular interest is the fact that patients treated with Calcitriol and Paricalcitol show a reduction in PTH levels, yet maintain high levels of FGF23. PTH serves as a marker for the rate of bone remodeling in patients, where elevated levels indicate renal bone disease. The analysis of FGF 23 is crucial in evaluating cardiovascular risk.

Keywords: secondary hyperparathyroidism, calcium, phosphorus, alkaline phosphatase, fibroblast growth factor 23

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Introduction

Secondary hyperparathyroidism is a complication that begins in the early stages of chronic kidney disease. Its severity typically correlates with the extent and duration of renal insufficiency. This condition is associated with bone metabolism disorders, calcium deposition in vessels and organs, and a substantially higher risk of cardiovascular diseases and mortality. It is established that it influences hematopoiesis, the immune response, the energy balance of the central nervous system, and it affects the cognitive functions.[1,2]

The factors contributing to the development and progression of secondaryhyperparathyroidism are being progressively clarified over the years:

In 1937, the American endocrinologist Fuller Albright established a link between chronic kidney disease and parathyroid gland hyperplasia, coining the term osteitis fibrosa cystica.

Approximately during the same period, the first laboratory tests were developed to determine serum PTH concentrations. It was believed that hypocalcemia played a leading role in this condition. Unfortunately, the long-term experience with treatment using high doses of calcium has not yielded the desired results, as it has little effect on PTH levels and worsens cardiovascular risk.

In 1969, Erwin Reiss presented the first experimental data on the role of phosphorus and thebeneficial effects of a low-phosphate diet in treating secondary hyperparathyroidism.

In 1971, the significance of 1-25 Vitamin D3 for the progression of bone disease and secondary hyperparathyroidism was established. This led to the introduction of treatment with Calcitriol and its analogs, which remains the foundation of treatment for secondary hyperparathyroidism to this day. In recent years, the fibroblast growth factor FGF 23 has beenincreasingly recognized for its role in regulating calcium/phosphorus homeostasis and hyperparathyroidism, as well as its relationship to vascular calcification and left ventricular hypertrophy.[3,4]

FGF23 is a peptide hormone synthesized by osteocytes and osteoblasts. It is the primary hormone that regulates blood phosphate levels, achieved by stimulating phosphaturia through its interaction with a dimeric receptor—FGF-receptor and the co-receptor Klotho. Activationof the Klotho-receptor in the kidneys leads to the inhibition of renal phosphate transporters Na Pi2a and Na Pi2c in the proximal tubule. Additionally, FGF 23 suppresses renal alpha-1 hydroxylase activity.

The increase in FGF 23 begins in the early stages of Chronic Kidney Disease and precedes the laboratory detection of hyperphosphatemia. Its elevation can result not only from hyperphosphatemia in Chronic Kidney Disease but also from active hematologic or oncologicdiseases associated with cellular breakdown and high levels of Interleukin 6.

In hemodialysis patients, hyperphosphatemia has traditionally been connected to higher mortality rates. Interestingly, this also holds for pre-dialysis patients and even the general population, where upper-limit serum phosphate levels are associated with higher cardiovascular risk. A similar correlation is observed with elevated serum levels of FGF 23.

Recent understanding of the mechanisms of vascular damage associated with hyperphosphatemia and high FGF 23 levels points to the following aspects: The main harmful factor in hyperphosphatemia, contributing to heightened cardiovascular risk, is vascular calcification. In vitro research on cultured human vascular smooth

muscle cells indicates that an increase in serum phosphorus levels enhances cellular calcification. Thepathogenic mechanism involves a change in the cellular genetic profile—transforming muscle cells into bone-forming cells.[5]

Modern studies have identified that hyperphosphatemia is associated with endothelial dysfunction. *In vitro* studies demonstrate that FGF23 induces dose-dependent hypertrophy ofcardiomyocytes. This activation occurs through FGF receptors and is independent of Klotho.[6]

A low-protein diet slows the progression of kidney disease, especially in patients with proteinuria. A protein-restricted diet reduces phosphorus intake, which is directly related tothe progression of kidney disease and decreased mortality.

After the start of dialysis treatment, dietary protein intake should be increased.[7] Hemodialysis patients on a high-protein diet have improved survival rates, as shown in the **HEMO study.** However, high protein intake is associated with higher phosphorus intake, which is linked to increased cardiovascular mortality. Therefore, adequate protein intake should be adjusted to include phosphorus restriction in the diet.

One gram of protein contains 13–15 mg of phosphorus, of which 30–70% is absorbed through the intestines. Thus, consuming 90 g of protein per day results in the absorption of 600–700 mg of phosphorus daily. In hemodialysis, the net positive phosphorus balance over48 hours is 1200–1400 mg, with only 500–600 mg being eliminated per dialysis session.

Phosphorus in food comes in various forms. Organic phosphorus associated with proteins has low absorption rates. Conversely, inorganic phosphorus found in supplements and preservatives is highly absorbable, with rates above 90%. These phosphate additives are a key ingredient in industrially processed foods, helping to extend shelf life, inhibit microorganism proliferation, and improve taste. Inorganic phosphate is well absorbed in the intestines, often resulting in hyperphosphatemia.

Organic phosphorus from plant protein has lower absorption compared to phosphorus from animal protein. This is because phosphorus in plants is in the form of phytates, while mammals lack phytases.

Phosphorus in animal protein is in the form of organic phosphate, which is easily hydrolyzed and absorbed. Not all animal proteins contain the same proportion of phosphorus. Adequate food labeling requires the indication of the ratio of phosphorus (in mg) to protein (in grams).Cheese and soft drinks have a high phosphorus-to-protein ratio. Presenting this ratio is recommended by KDIGO guidelines, drawing attention to phosphorus-rich foods.

Materials and Methods

We present a study of 110 patients treated in the nephrology department of Acibadem City Clinic Tokuda Hospital from 2022 to 2024, analyzing the relationship between FGF 23 and PTH levels in relation to eGFR, calcium, phosphorus, andALP levels.

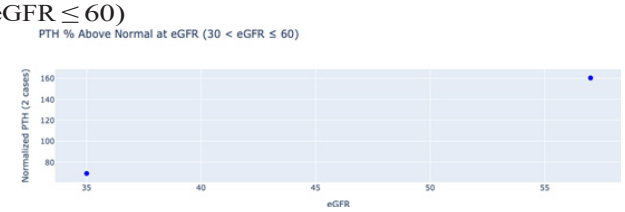
The statistical methods employed in this study include interval estimations, Linear Regression, Ridge Regression, and Partial Regression. Each method was chosen based on the task and the specific requirements indicated by the data characteristics and the statistical matrices.

The serum concentration of FGF 23 total was measured using Simple Plex ™ assay (Ella ProteinSample, USA). This assay recognizes natural and recombinant human FGF-23. The linearity of the test is between 3.78 and 36000 pg/ml. The intact PTH was measured with CMIA method on iAlinity Analyzer (Abbott Diagnostics, USA). For the calculation of eGFRis used CKD-EPI 2012 formula.[8]

With an eGFR ranging from 30 to 60, what is the average percentage increase of PTH and FGF23 above normal levels?

PTH

Average PTH value above normal: 114.71% for the eGFR range greaterthan 30 and less than or equal to 60. ($30 < eGFR \leq 60$)



A concern persists that our sample includes only two cases with an eGFR greater than 30 andless than or equal to 60.

FGF23

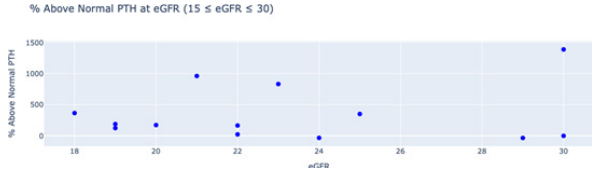
Average FGF23 value above normal: 182.06% for the eGFR rangegreater than 30 and less than or equal to 60. ($30 < eGFR \leq 60$)

The issue remains that there are only two cases in the sample with an eGFR greater than 30and less than or equal to 60.

At an eGFR between 30 and 15, how much above normal are PTH and FGF23 on average?

PTH

Average PTH value above normal: 345.59% for the interval with eGFRgreater than or equal to 15 and less than or equal to 30. ($15 \leq eGFR \leq 30$).



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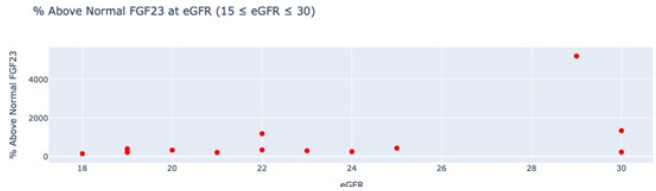
FGF23

Average FGF23 value above normal: 812.16% for the interval with eGFR greater than or equal to 15 and less than or equal to 30. (15 ≤eGFR ≤ 30).

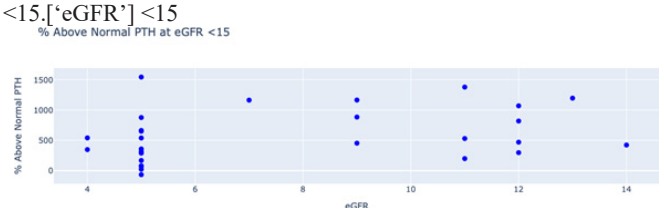


We observe that the high average value of FGF23 is partly due to 3 statistical outliers—thethree highest points, which are over 1000% above the normal level. The other cases range between 200% and 350% above normal.

For eGFR below 15, what is the average percentage above normal for PTH and FGF23?

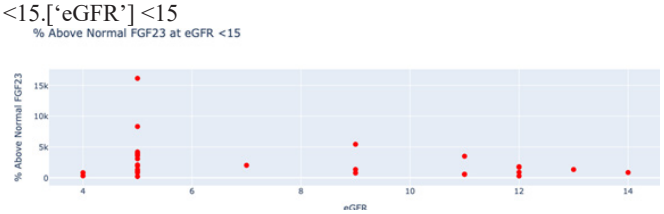
PTH

Average PTH value above normal: 586.50% for the eGFR range <15.['eGFR'] <15



FGF23

Average FGF23 value above normal: 2588.22% for the eGFR range <15.['eGFR'] <15



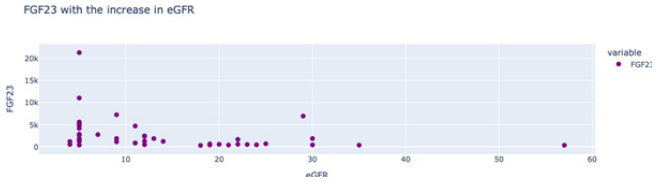
Summary of the points presensted till here:

	30 <eGFR <=60	15 <=eGFR <=30	['eGFR'] <15
PTH	115%	345,59%	586,50%
FGF23	182,06%	812,16%	2588,22%

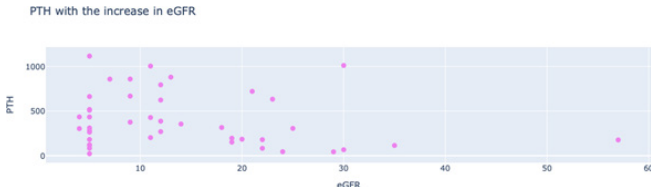
Graph showing the trends of PTH and FGF23 as eGFR decreases

The graphs should be interpreted from right to left, as they represent the increase in eGFR.

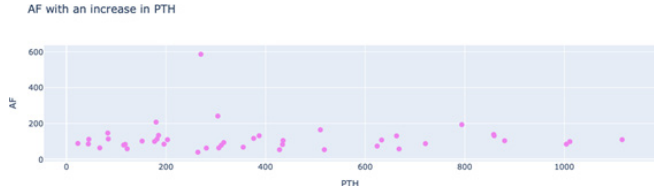
FGF23



PTH



Does alkaline phosphatase change with an increase in PTH?



The graph shows the relationship between AF and PTH. The horizontal axis represents thevalue of PTH, while the vertical axis represents AF.

Key observations

Lack of a clear linear relationship: At first glance, there is no clearly expressed linear dependence between PTH and AF. The values of AF vary over a wide range at different PTH values, indicating that an increase in PTH does not lead to a proportional increase or decrease in AF.

Exceptions (outliers): There are several points with high values of AF that significantly deviate from the other data, especially around PTH values in the range of 600-700. These observations may be potential outliers and might deserve further analysis.

Concentration of data: Most of the points are located in the PTH range between 0 and 500, while AF remains in the range below 200. This suggests that for most cases, regardless of the PTH value, AF does notincrease significantly.

Discussion

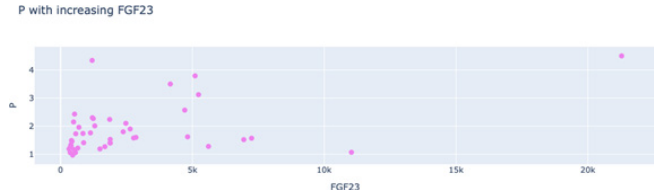
There is no strong linear relationship between PTH and AF based on this graph. Other factorsmay be influencing AF, or the relationship between these two variables may not be linear.

However, with the variables at our disposal, there appears to be no clear relationship betweenPTH and AF.

Is there a relationship between the increase in FGF 23 and the values of P?

Answer: Yes, according to the data, it can be seen that there is a positive relationship.

Evidence:



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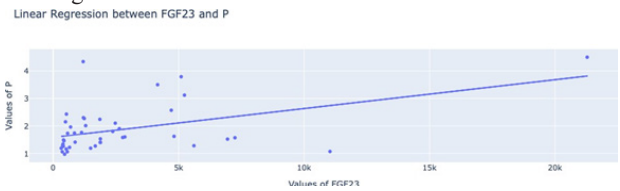
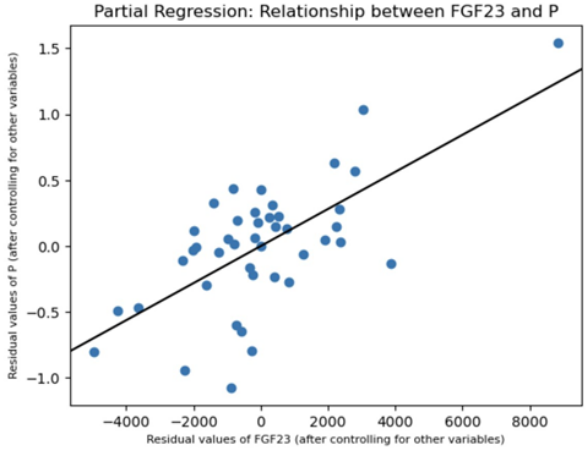
A positive relationship is observed between the two variables. Linear regression is used toexamine the relationship between FGF23 and P, scaling the values of FGF23 for better interpretation and visualizing the results.



These results allow us to assert that there is a positive linear relationship between P and FGF23. This can also be demonstrated with Partial regression, which you can see here:



This graph represents a partial regression between the variables FGF23 and P, controlling forthe effect of the other variables in the model.

Interpretation

i. **The X-axis shows the residual values of FGF23** after controlling for the other variables. This means that the influence of the remaining variables has been removed,and we are only seeing the portion of FGF23 that is not explained by them (controlling for autocorrelation).

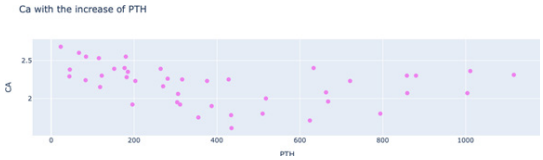
ii. **The Y-axis shows the residual values of P** after controlling for the same other variables, meaning that here we also see only the portion of P that is not influenced bythe other variables.

iii. **The black line on the graph represents the regression line**, which shows the linear relationship between FGF23 and P after removing the influence of the other variables.The positive slope of the line suggests that there is a positive relationship between FGF23 and P— as the residual values of FGF23 increase, the residual values of P alsoincrease.

Conclusion

The graph shows that after controlling for the other variables, there is a positive relationshipbetween FGF23 and P, which means that P may have a statistically significant effect on FGF23 in the context of this model.

Is there a relationship between the increase in PTH and the levels of Ca?



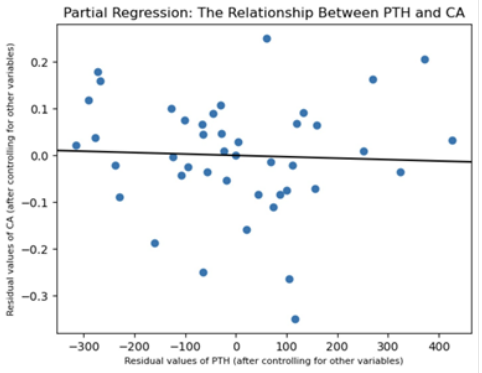
This graph displays the values of PTH (on the X-axis) and Ca (on the Y-axis), with each pointrepresenting an observed data value. Possible relationship between the two variables:

a) The graph suggests no clear linear relationship between PTH and Ca. The points arescattered, with Ca values remaining relatively stable around 2.0–2.5, even as PTH values vary widely (from 0 up to over 1000).

b) There may be a slight negative slope in certain sections of the data (e.g., at lower PTHvalues) where Ca values decrease as PTH increases, but this is not a pronounced trend.

c) At moderate and high PTH levels (above 400), Ca values remain relatively constant, suggesting that increases in PTH do not significantly affect Ca levels in this range.

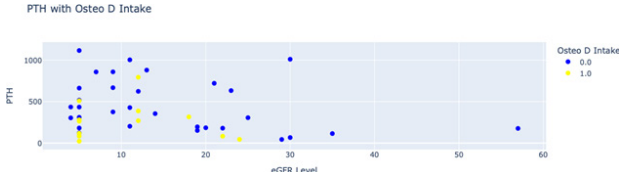
The same result is observed in the partial regression, which you can view here:



Based on the presented regression results, we can conclude that there is no statistically significant relationship between PTH and the dependent variable in this model. This findingis consistent with the visualization, which shows no clear link between PTH and CA. The results also highlight the significance of other variables, suggesting that there may be other factors impacting the health indicators being studied.

Is there a smaller increase in PTH and FGF23 among patients taking calcitriol/Osteo D compared to those with the same eGFR who are not taking it?

PTH:



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The graph shows the relationship between PTH (on the Y-axis) and eGFR (on the X-axis),with points colored based on the value of the binary variable "Calcitriol Intake." In the legend, yellow points correspond to PriemVD = 1 (intake of Calcitriol), while blue points indicate PriemVD = 0 (no Calcitriol intake).

Analysis of the graph

Distribution of PTH relative to eGFR

1. The values of PTH show high variability, with PTH reaching values above1000 at lower eGFR levels (below 20).
2. As eGFR increases (between 20 and 60), PTH values become more dispersed,and in these ranges, there are fewer extreme high values of PTH.

Color distribution (Calcitriol intake)

1) The yellow points, representing patients taking Calcitriol, predominantly appear at lower PTH values (below 500) and are found across various eGFRranges.
2) The blue points (PriemVD=0) are present over a wider range of PTH values,including those above 1000. This may suggest that patients not taking Calcitriol tend to have higher PTH levels.

The results of the linear regression present a model that examines the influence of various variables, including eGFR, on PTH levels. The main goal of the analysis is to determine whether the intake of Osteo D leads to different PTH levels while controlling for other factorssuch as eGFR and FGF23.

Key observations

Coefficient of Osteo D (Calcitriol): The coefficient for PriemVD from the linear regression (OLS) is -257.8232 with a p-value of 0.049, which is statistically significant at the standard threshold of 0.05. This means that among patients who take Calcitriol, the levels of PTH are, on average, about 257 units lower compared to those whodo not take the supplement, after controlling for other variables.

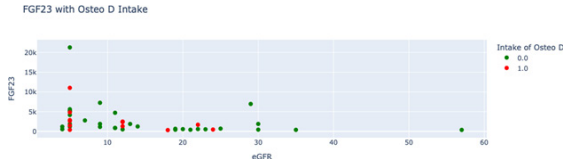
This suggests that the intake of Calcitriol has a significant effect on reducing PTH, regardlessof other factors such as eGFR (the effect of Calcitriol on PTH has been analyzed under the assumption that the level of eGFR is the same for all patients or that the influence of eGFR has been accounted for).

Even if the model does provide a statistically significant result, it is important to mention that autocorrelation has been noticed between the variables. For this reason we ran a second regression (Ridge regression) with the scope of adjusting the coefficients for the autocorrelation.

In the Ridge regression model, the coefficient for Osteo D (intake of Calcitriol) for PTH is -52.29. This means that patients taking Osteo D have lower levels of PTH (on average about 52.29 units lower), while controlling for other variables, including eGFR.

Even if the coefficient seems to be lower, it does confirm the theory that the intake ofCalcitriol has an effect on reducing PTH, regardless of other factors such as eGFR.

FGF23:



The graph shows the values of FGF23 relative to eGFR (kidney function), with the points divided into two groups: patients who take Calcitriol (in red) and those who do not (in green).Hee we analyze how the intake of Calcitriol affects the levels of FGF23 while keeping eGFR constant.

Observations from the graph

Low values of eGFR (below 10): It can be seen that both patients who take Calcitriol and those who do not havelarge variations in FGF23 levels. Although there are several patients with high levels of FGF23 (above 10k) among both the Calcitriol group and the non-Calcitriol group at low eGFR values, there is no clear trend indicating that the intake of Calcitriol leads tolower levels of FGF23 in this category.

Average values of eGFR (between 10 and 30): In this range, there are fewer patients with high levels of FGF23. The group of patients who take Calcitriol and those who do not seem to havesimilar levels of FGF23, with values below 5k. This may indicate that at average eGFR values, the intake of Calcitriol does not have a significant effect on FGF23 compared to patients who do not takeit.

High values of eGFR (above 30): At these eGFR values, the levels of FGF23 are relatively low. In this range we do not have patients who take Osteo D, therefore it is not possible to discuss the impact of Osteo D on the levels of FGF23. The graph fails to demonstrate a clear trend indicating that patients who take Calcitriol experience a significantly smaller increase in FGF23 compared to those who do not, at equivalent eGFR levels. While there are fluctuations in FGF23 levels, the differences between the groups are not substantial enough to draw a conclusion that Calcitriol has asignificant impact on FGF23 when eGFR is held constant.

With the help of regression analysis, we demonstrate the aforementioned points:

- Coefficient: 1566.77, P-value: 0.230
- The coefficient indicates that patients who take Calcitriol tend to have higher levels of FGF23 (approximately 1566.77 units more), but the P-value is not statistically significant (indicating that the coefficient representing the relationship is not statistically significant). This means we cannot conclude with certainty that Calcitriol intake affects FGF23 in this model.

Due to the high coefficient levels and issues with multicollinearity, we again use Ridge Regression to verify the results. After regularization (the Ridge regression), the coefficient for Osteo D becomes negative, suggesting a slight decrease in FGF23 for patients who takeCalcitriol compared to those who do not. However, this coefficient is relatively small and likely has no significant weight in the overall context of the model.

Conclusion

In both models (OLS and Ridge), there is no significant evidence that the intake of Calcitriolleads to significantly lower or higher levels of FGF23 in patients with the same eGFR.

What conclusions can we draw from the conducted studies

a) Hyperphosphatemia plays a leading role in the increase of PTH and FGF23.

b) PTH is the main marker for determining the rate of bone remodeling and increaseswith the progression of CKD (chronic kidney disease).

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c) FGF23 is a marker for assessing the risk of vascular calcifications and cardiovascular complications and increases with the progression of CKD.

d) A low-phosphate diet and treatment with phosphate binders play a significant role in reducing the risk of cardiovascular complications in patients with CKD.

e) Patients undergoing treatment with Calcitriol and its analogs have a reduced risk ofdeveloping renal bone disease but not of cardiovascular complications.

f) The level of alkaline phosphatase (ALP) indicates the number of osteoblasts and osteoblast-like cells and has a direct relation with osteoporosis and the risk of fractures. It does not correlate with the level of PTH.

Acknowledgments

None.

Conflicts of interest

Author's deciare that there is no conflict of interests.

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