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Level of Phosphorus in Patients with Chronic Kidney Disease

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ABSTRUCT

Serum phosphorus levels stay relatively constant through the influence of multiple factors ,such as parathyroid hormone, fibroblast growth factor 23, and vitamin D on the kidney, bone, and digestive system. Whereas normal serum phosphorus ranges between 3 mg/dL to 4.5 mg/dL, large cross-sectional studies have shown that even people with normal kidney function are sometimes found to have levels ranging between 1.6 mg/dL and 6.2 mg/dL. While this may partially be due to diet and the factors that control phosphorus homeostasis , total understanding of these atypical ranges of serum phosphorus remains uncertain. Risks for bone disease are high in people aged 50 and older, and this group comprises a large proportion of people who also have chronic kidney disease.

Consuming diets low in calcium and high in phosphorus, especially foods with phosphate additives, further exacerbates bone turnover. Existing bone disease increases the risk for high serum phosphorus, and higher serum phosphorus has been associated with increased adverse events and cardiovascular-related mortality both in people with chronic kidney disease and in those with no evidence of disease. Once kidney function has deteriorated to end-stage disease (Stage 5), maintaining normal serum phosphorus requires dietary restrictions, phosphate-binding medications, and dialysis. still, normal serum phosphorus remains elusive in many patients with Stage 5 kidney disease. Protecting and monitoring bone health should also aid in controlling serum phosphorus as kidney disease advance.

AIM OF THIS STUDY

The aim of this study is evaluate the level of phosphorus in CKD and to aid in the diagnosis of conditions known to cause abnormally high or low levels of phosphorus.

CHAPTER ONE

INTRODUCTION

INTRODUCTION

Phosphorus is mineral that combined with other substance to form organic and inorganic phosphorus compounds. The terms phosphorus and phosphate are often used interchangeable when talking about testing , but it is the of inorganic phosphate in the blood.

The body needs phosphorus to build and repair bones and teeth, help nerves function, and make muscles contract. Most (about 85%) of the phosphorus contained in phosphate is found in bones. The rest of it is stored in tissues throughout the body. The kidneys help control amount of phosphate in the blood[(1).]

A Chronic kidney disease (CKD) is a type of kidney disease in which there is gradual loss of kidney function over a period of months to years. Sins, chronic kidney disease emerging as one of the major public health problems across the world and its incidence is rising day by day .CKD may lead to end stage renal disease (ESRD)and is also associated with increase risk of cardiovascular disease ,heart disease and increase health care expenditures[(7).]

Normal working kidney can remove extra phosphorus in your blood when you have chronic kidney disease extra phosphorus cause body changes to pull the calcium outer the bones make them week. High phosphorus and calcium level also lead to dangerous calcium deposited in blood vessels ,lung ,eyes and heart[(8)]. Serum phosphorus level is decrease in patient with hyperthyroidism and in hypovitaminosis (Rickets and osteomalasia[(7)]), Phosphorus increase in kidney disease , hypervitaminosis and in hypoparathyroidism[(10)].In large cross-sectional population studies, mean serum phosphorus (or inorganic phosphate, iP) remains fairly constant at approximately 3.8 mg/dL in subjects with normal kidney function. It does the same in those with impaired kidney function until the glomerular filtration rate (GFR) falls to below 30 mL/min/1.73 m^2—which represents Stage 4 chronic kidney disease (CKD)[(9)]. At this point serum phosphorus levels start to rise and continue rising as these patients reach end-stage kidney disease (ESRD, Stage 5)[(1)]. The relative constancy of the serum phosphorus in normal and early kidney disease is maintained by the interaction of multiple factors including parathyroid hormone (PTH), fibroblast growth factor 23 (FGF 23), vitamin D, and others acting on the gut, kidneys, and bone[(3)].

CHAPTER TWO

LITERATURE REVIEW

Literature Review

Daily phosphorus ingestion is approximately 1200 mg, of which 950 mg are absorbed. Around 29% of body phosphorus is located in bone, and less than 1% is in the blood, which is the phosphorus that is quantified in clinical practice. Most phosphorus (70%) is located intracellular and is interchangeable. Phosphorus is removed by two systems, the gastrointestinal tract, (150 mg/day) and the urine (800 mg/day)[(2).]

Ingestion of phosphorus by an individual with normal renal function results in immediate phosphaturia probably mediated by phosphatonins of intestinal origin[(3).]

Serum phosphorus levels stay relatively constant through the influence of multiple factors, such as parathyroid hormone, fibroblast growth factor 23, and vitamin D on the kidney, bone, and digestive system[(7)].

Mineral metabolism has emerged as important predictors of morbidity and mortality in dialysis patients . Disturbutionces in phosphorus is commonly observed in patients with chronic kidney disease .renal osteodystrophy ,metabolic bone disease usually accompanies CKD[(4).] For which numerous drugs including phosphorus binders, vitamin D compounds, and calcimimetic agents have been specifically developed and promoted[(5,6)] . Elevated phosphorus levels correlates with increased risk for vascular calcification in humans with advanced chronic kidney disease (CKD).

If the test shows high levels of phosphate/Phosphorus levels it may mean the patient have;

- Kidney disease, your body can't remove phosphate from your blood quickly enough[(9)].
- Hypoparathyroidism, in which parathyroid gland does not make enough parathyroid hormone levels[(9)].
- High vitamin D levels.

- Diabetic ketoacidosis, a life threatening complication of diabetes in which high levels of acids called ketones in the blood of people with diabetes[9].
- High dietary phosphate.

If Serum phosphorus test show that patient have low phosphate/phosphorus levels, it may mean the patient have;

- severe malnutrition, such as from anorexia or starvation[10] .
- alcoholism
- severe burns
- a diabetes complication called diabetic ketoacidosis
- the kidney disorder, Fanconi syndrome
- an excess of parathyroid hormone (hyperparathyroidism)[10] .
- chronic diarrhea
- vitamin D deficiency (osteuomalacia).

The amount of phosphate in the blood affect the level of calcium in the blood .Calcium and phosphate in the body react in opposite ways :as blood calcium levels rise, phosphate levels fall. A hormone called parathyroid hormone (PTH) regulates the levels of calcium and phosphorus in your blood. When the phosphorus level is measured ,a vitamin D level ,and sometimes a PTH level ,is measured at the same time. Vitamin D is needed for your body to take in phosphate[11] .

Nephrology guidelines recommend targets and treatment strategies to correct serum levels of phosphorus, calcium, and parathyroid hormone because observational data suggest there is an association between these potential risk biomarkers and vascular disease and death[6] .

The nephrologists may order to patients with chronic kidney disease a medicine called a phosphate bindorus, the amount of phosphorus binder take with meals and snacks. This medicine will help to control the amount of phosphorus[8] .

2.1 Phosphate homeostasis

Phosphorus is an essential element and plays an important role in multiple biological processes[12] . Phosphorus-containing compounds have important roles in cell structure (maintenance of cell membrane integrity and nucleic acids), cellular metabolism (generation of ATP), regulation of subcellular processes (cell signaling through protein phosphorylation of key enzymes), maintenance of acid–base homeostasis (urinary buffering), and bone mineralization[13,14] . Therefore, the maintenance of appropriate phosphorus homeostasis is critical for the well-being of the organism and for an optimal calcium–phosphate product for the mineralization of bone without its deposition in vascular and other soft tissues. In biological systems, phosphorus is present as phosphate, and these two terms are commonly used interchangeably.

Phosphate is the most abundant anion in the human body and comprises approximately 1 % of total body weight[15] . It is a predominantly intracellular anion where its concentration is 100-fold greater than that in the plasma. The majority of phosphate is present in bone and teeth (85 %), with the remainder distributed between other tissues (14 %) and extracellular fluid (1 %). In the skeleton, phosphate is primarily complexed with calcium in the form of hydroxyapatite crystals; the remaining phosphate appears as amorphous calcium phosphate [15]. In soft tissue and cell membranes, phosphorus exists mainly as phosphate esters and to a lesser extent as phosphoproteins and free phosphate ions. In the extracellular fluid, about one-tenth of the phosphorus content is bound to proteins, one-third is complexed to sodium, calcium, and magnesium, and the remainder is present as inorganic phosphate [13] .

Serum phosphate concentration varies with age, with the highest concentration being in infants [normal range 4.5–8.3 mg/dL (1.50–2.65 mmol/L, conversion factor 0.322], who require more of the mineral for bone growth and soft tissue buildup, and concentrations declining towards adulthood [normal range 2.5–4.5 mg/dL (0.8–1.5 mmol/L)][12,16] . Accordingly, in both the intestinal tract and the kidney, there is an age-related decline in phosphate absorption and reabsorption, respectively, that is correlated with decreased gene and protein expression of sodium–phosphate co-transporters[17] .

In human adults, under steady state conditions, a regular Western diet provides between 1000 and 1,600 mg/day (approx. 20 mg/kg/day) of

phosphorus[18] . Of this, approximately 16 mg/kg/day is absorbed in the proximal intestine, predominantly in the jejunum. Approximately 3 mg/kg/day is secreted into the intestine via pancreatic, bile, and intestinal secretions, giving a net phosphorus absorption of approximately 13 mg/kg/day, while 7 mg/kg/day appear in the feces[12] .

Until not too long ago, only three main regulators of phosphate metabolism had been identified;
(1) dietary phosphate intake and absorption
(2) calcitriol, which increases phosphate absorption from the gut and bone
(3) parathyroid hormone (PTH) which directly causes phosphate resorption from bone and decreases its reabsorption in the proximal tubule, and indirectly by stimulating the production of calcitriol.

However, more recent findings have also demonstrated the physiological importance of bone and phosphatonins, such as fibroblast growth factor-23 (FGF-23) in phosphate regulation[21] .

2.2 Hormones involved in phosphate homeostasis

2.2.1 Parathyroid hormone

The primary function of PTH is to tightly regulate serum calcium concentration. In this regard, hypocalcemia stimulates the parathyroid glands to produce and release the hormone. PTH increases proximal tubular expression of 25(OH)D 1α-hydroxylase, resulting in increased production of $1,25(OH)_2D_3$ and, consequently, increased calcium absorption in the gut. PTH also enhances calcium reabsorption in the distal convoluted tubule [15] . In the bone, PTH stimulates the release of calcium into the extracellular fluid by increasing osteoclastic bone resorption . In addition to its effects on calcium, PTH is one of the best characterized hormonal regulators of plasma phosphate concentration. delivery of PTH results in reduced expression of NaPiIIa and NaPiIIc in the apical membrane of the proximal tubule[19] . PTH decreases renal phosphorus reabsorption by binding to a type 1 PTH receptor in the proximal tubular cells, by stimulating cAMP synthesis and the phospholipase C pathway and inducing the retrieval of the NPT2a co-transporter from the brush border membrane of the proximal tubular cells with the presence of the sodium proton exchanger regulatory factor 1 (NHERF1) . The exact role of PTH on the NPT2c co-transporter is not completely elucidated .[21,23,24]

2.2.2 Calcitriol

Whereas PTH is one of the strongest stimulators of $1,25(OH)_2D_3$ production, the latter acts to suppress PTH. Thus, $1,25(OH)_2D_3$ not only largely regulates serum phosphate concentration directly by increasing its intestinal absorption but also indirectly by increasing its tubular reabsorption through its suppression of PTH. The opposing effects of PTH and vitamin D on the kidney and the intestine, respectively, balance phosphate levels while preserving calcium ion homeostasis. These two regulators are tightly intertwined with FGF-23 physiology[(15)].

2.2.3 Fibroblast growth factor-23

FGF23 is a 32 kDa protein secreted by osteocytes in bone and regulates phosphorus and vitamin D metabolism. Its main stimuli are high phosphorus intake, 1,25 vitamin D and perhaps PTH (directly, or through an increase of 1,25 vitamin D)[(20,21,22)] . On the contrary, increased serum phosphorus is not a stimulus for FGF23, as it has been observed in the hyperphosphatemia of primary hypoparathyroidism (low PTH and high FGF23 serum levels), indicating that its primary role is net phosphorus balance and not phosphorus serum levels[(21)] .

2.2.4 FGF23 and Phosphorus transporters

FGF23 decreases NPT2a and NPT2c co-transporters RNA and protein expression in the kidney and NPT2b in the intestine. The effect of FGF23 on NPT2b in the intestine is mediated through the reduction of calcitriol levels by the FGF23, as it inhibits 1-á hydroxylase expression in the proximal renal tubule and stimulates the enzyme 24 hydroxylase, that inactivates calcitriol and 25-OH vitamin D. In addition recent data indicate an inhibitory role of FGF23 on the secretion of PTH by the parathyroid glands which can also influence phosphorus excretion.[(20,21,25)]

2.3 Phosphorus metabolism in chronic kidney disease

The knowledge about the exact mechanisms involved in phosphorus homeostasis and the evolution of secondary hyperparathyroidism in chronic kidney disease (CKD) has improved during the last years. The discovery of Fibroblast Growth Factor 23 (FGF23) has revolutionized our understanding about the links between mineral metabolism, vitamin D and parathyroid hormone (PTH). FGF23 serum levels increase early in CKD before the increase of serum phosphorus or the decrease of vitamin D and there is parathyroid resistance to FGF23 in advanced CKD. Increased levels of serum phosphorus have been related in epidemiological studies with adverse outcomes in patients with CKD, diabetes, coronary artery disease, or even normal adults. In patients with CKD stage 3 or 4, low phosphorus diets have been related with adverse outcomes due to the risk of malnutrition and there are limited data regarding the role of phosphate binders in these patients. Recent studies suggest that increased serum FGF23 levels are associated with mortality, left ventricular hypertrophy and progression of CKD independently of serum phosphorus levels. There is an ongoing debate about the "normal" or "desirable" levels of serum phosphorus in CKD and a new role of FGF23 as a marker of the disturbances of mineral metabolism in CKD is emerging.[23]

High serum levels of FGF23 have been associated with increased left ventricular mass[26], increased arterial stiffness[27] and more rapid decline of renal function[28], although its relation with vascular calcification remains rather conflicting[21]. It should be noted that in all these studies the effect of FGF23 was independent of serum phosphate levels indicating that perhaps FGF23 is superior to serum phosphorus levels as a marker of morbidity or mortality in CKD patients[21,29].

As vitamin D increases FGF23 levels it would sound logical that this kind of therapies might be detrimental for CKD patients. However there are conflicting data, as increased FGF23 serum levels have been associated with increased mortality, whereas vitamin D treatment have been associated better survival in HD patients[21].

2.4 Phosphorus and Nutrition in Chronic Kidney Disease

Patients with renal impairment progressively lose the ability to excrete phosphorus. Decreased glomerular filtration of phosphorus is initially compensated by decreased tubular reabsorption, regulated by PTH and FGF23, maintaining normal serum phosphorus concentrations. There is a close relationship between protein and phosphorus intake. In chronic renal disease, a low dietary protein content slows the progression of kidney disease, especially in patients with proteinuria and decreases the supply of phosphorus, which has been directly related with progression of kidney disease and with patient survival.

2.4.1 Protein Intake and Phosphorus;

There is a close relationship between protein and phosphorus intake[(30)] . Proteins are rich in phosphorus so most of the scientific societies recommend reducing protein intake from early stages in patients with chronic renal failure, to reduce the input of phosphorus. One gram of protein has 13–15 mg of phosphorus of which 30–70% is absorbed through the intestine. Thus, an intake of 90 g of proteins a day results in absorption of 600–700 mg of phosphorus daily. In hemodialysis the net positive phosphorus balance in 48 hours is 1200–1400 mg/day, of which dialysis only removes 500–600 mg/session. Thus, there are two good reasons to restrict protein intake in chronic renal disease. On one side, a low dietary protein content slows the progression of kidney disease, especially in patients with proteinuria[(31)] . In addition ,a protein-restricted diet decreases the supply of phosphorus, which has been directly related with progression of kidney disease and with patient survival. A restricted protein diet has additional advantages .In advanced chronic kidney disease (CKD) most guidelines recommend a diet containing 0.6 to 0.8 g protein/kg/day based on meta-analysis demonstrating its efficacy .This restriction is safe nutritionally and metabolically, After initiating dialysis the dietary protein intake should be increased[(32)] .

2.4.2 Phosphorus Absorption and Protein of Different Origins:

Phosphorus in foods is found in different forms. Organic phosphorus associates with proteins has a low absorption. By contrast absorption of inorganic phosphorus found in additives and preservatives is very high, above 90%. A large amount of phosphate are added to foods as preservatives as well as from common beverages such cola, with a high phosphate content [(33)] . However, organic phosphorus from plant protein has a lower absorption than phosphorus from animal protein.
In a crossover trial, patients with CKD stages 3-4 ingested a diet with animal or vegetable protein for 7 days. Animal protein intake increased serum phosphorus and FGF23 more than vegetable protein intake [(34)] . The simple recommendation is to reduce preservatives and additives in the first place, favor foods rich in vegetables, reduce meat, and avoid convenience foods.

Adequate labeling of food requires showing the ratio of phosphorus (in mg) to protein (in grams). The ratio ranges from <10 to >65 mg/g.
However, this ratio does not provide information on the bioavailability of phosphorus from different sources. Patients with CKD should be prescribed a low phosphorus, low inorganic phosphorus and low phosphorus/protein ratio diet, and with a proper protein content to improve the attractiveness of food[(35)] .

2.4.3 Low-Protein Diet and Malnutrition

The diet in patients with advanced-stage CKD has been controversial throughout the history of Nephrology. CKD is associated with protein calorie malnutrition [(37)] . A diet with a too low-protein content can favor malnutrition and increase morbidity and mortality[(30)] . However a low-protein diet can slow the progression of renal disease. While normoproteinc or high-protein diet may increase uremic symptoms and hyperphosphatemia. A delicate balance should be sought. A low-protein diet in CKD has the following potential advantages, improves phosphorus control[(36)] , delays initiation of dialysis , does not increase the risk of protein malnutrition if accompanied by essential amino acid supplement[(38)] , does not increase mortality in patients with low-protein diet after starting dialysis[(39)] , and protects against oxidative stress which may aggravate progression of CKD .

In dialysis, protein intake should not be restricted despite a higher intake of phosphorus, since the risk of protein malnutrition and mortality exceeds that of hyperphosphatemia[36] .When dialysis patients are prescribed a low-protein intake, actual protein intake is frequently lower than expected, possibly because of the difficulty in implementing the diet. Thus, a recommended intake of 0.3–0.6 g/kg/day protein is estimated to result in an actual intake of 0.48–0.84 g/kg/day [38] .Implementation of a low-protein diet requires a dedicated staff, with nurses, dietitians, and a close monitoring by nephrologists. However, in hemodialysis patients net phosphorus balance on a normoproteinc diet is positive even after deducting the phosphorus removed during the dialysis session. Hemodialysis removes 800 mg phosphorus/session (2400 mg/week). Thus, a protein intake of 1 g/kg BW/day as recommended will result in an estimated weekly net balance of phosphorus of 2000 mg.

The association between low-protein intake and increased mortality in dialysis patients suggests that alternative methods are needed to reduce phosphorus absorption, since high phosphorus is associated with mortality. There are two main alternatives. One is the use of specific nutritional supplements high in energy and protein content, but low in phosphorus. This diet allows maintaining an adequate nutritional status, without altering the serum phosphorus, and without need for higher phosphorus binders[40] . The second alternative is nutritional education of the patient. This includes greater attention to additives and preservatives, to the contribution of phosphorus from different protein foods, so that the diet is based on low phosphorus/protein ratio ingredients, as well as the proper and early use of phosphorus binders [36] .

2.4.4 Phosphorus Binders

In a major retrospective study patients treated with phosphorus binders before entering dialysis and phosphate above 3.7 mg/dL, had a better long-term survival than those in whom binders were initiated after initiation of dialysis. Similar results were obtained when binder use in the first 90 days of dialysis was compared with later initiation of binders[41] . The authors speculated that the observation might be explained by modulation of direct effect of phosphorus or compensatory mechanisms such as FGF23 on patient survival[42] . However, this reduction in mortality was not observed in incident dialysis patients treated with calcium-containing binders, either calcium acetate or calcium carbonate[43] . Phosphorus binders lower serum phosphorus and also lower FGF23 levels. Indeed in early CKD binders

may result in reduced FGF23 levels in the absence of changes in serum phosphorus[44] .

2.5 Controlling Serum Phosphorus in ESRD:-

Clinicians use a three-pronged approach to controlling serum iP in dialysis patients: (1) removal of ultrafilterable and diffusible phosphorus with dialysis, (2) restriction of dietary phosphate intake, and (3) use of orally administered phosphate binders to limit the absorption from the intestinal contents of ingested phosphate. Despite these efforts, serum iP levels in one-third to one-half of all patients on dialysis run higher than 5.5 mg/dL [(46)].

While this is often attributed to patient nonadherence, there are a number of legitimate factors contributing to persistent hyperphosphatemia in dialysis patients, including the following:

1. The removal of phosphate during one hemodialysis session amounts to only 800 mg to 1,000 mg. Thus dialysis 3 times a week is insufficient to remove the recommended daily intake of phosphorus for patients requiring dialysis (≤1,000 mg/d) [(45)] .
2. It is extremely difficult to limit phosphate intake while attempting to meet the recommended daily protein intake for patients having chronic hemodialysis of 1.1 to 1.3 gm/kg body weight.
3. Many retail food products have highly bioavailable inorganic phosphate added as a preservative to maintain freshness. As mentioned earlier, these contribute to the patient's phosphate burden.
4. Patients on dialysis have to take multiple medications, and the phosphate binders add to the patient's pill burden.
5. Phosphate binders are generally large pills that are hard to swallow, or if chewed during a meal may distort the sense of taste, making adherence difficult. Furthermore, these medications often cause gastrointestinal upset and are variable in their phosphate-binding capacity.
6. Finally, two additional contributing factors have been highlighted, both related to measures used in the management of these patients. One is the administration of high doses of calcitriol, or its analogues, which are known to enhance active phosphate absorption from the small intestine.

   The other factor is the lowering of intestinal free phosphate concentration, whether by dietary phosphate restriction or with phosphate binders, which is a known stimulus to enhance phosphate

absorption from the small bowel. These two important factors impede the patient's efforts to control their phosphate burden.

All of the above considerations, but especially the last, have led investigators to consider intestinal active phosphate transport as a novel target for therapy. In mice with experimentally induced renal failure and hyperphosphatemia, the hyperphosphatemia was corrected by conditional knockout of the small intestine phosphate transporter, NaP2b, in combination with sevelamer to reduce passive phosphate absorption[(46)] .

A novel inhibitor of intestinal Na/H+ exchange has recently been shown to be effective in controlling hyperphosphatemia in a similar setting. In terms of a clinically available and effective therapy, nicotinamide, a widely used lipid-lowering agent, has been shown to inhibit NaP2b and lower serum iP in CKD patients[(45)] .

2.6 Bone Disease Prevalence and Contribution to Serum Phosphorus:-

Among micronutrients, calcium (Ca) and inorganic (i) phosphate (P) are the two main constituents of hydroxyapatite, the bone mineral that strengthens the mechanical resistance of the organic matrix. Bone contains about 99% and 80% of the body's entire supply of Ca and P, respectively. The Ca/P mass ratio in bone is 2.2, which is similar to that measured in human milk[(47)] .

Both Ca and Pi positively influence the activity of bone-forming and bone-resorbing cells. Pi plays a role in the maturation of osteocytes, the most abundant cells in bone. Osteocytes are implicated in bone mineralization and systemic Pi homeostasis. They produce fibroblast growth factor-23, a hormonal regulator of renal Pi reabsorption and 1,25-dihydroxy vitamin D production. This relationship is in keeping with the concept proposed several decades ago of a bone-kidney link in Pi homeostasis.

Bone health is dependent on dietary intake of vitamins and minerals. Three major bone nutrients are calcium, phosphorus, and vitamin D. During growth and development, only one-fourth to one-third of dietary calcium is absorbed and almost entirely stored in bones and teeth. In contrast, approximately 70% of dietary phosphorus is absorbed, and the amount of absorption depends on the type of phosphorus: 30% to 70% of the phosphorus found naturally in foods is absorbable[(47)] , whereas 100% of phosphorus from inorganic phosphate additives is absorbable[(48)] .
The rate of bone remodeling is important in determining the concentration of plasma phosphorus, as disproportionate increased bone resorption will lead to a higher plasma phosphorus concentration whereas increased mineralization will lead to a lower one . An example of the latter is the condition termed “hungry bones”, which follows parathyroidectomy in patients with secondary hyperparathyroidism. Unlike plasma calcium, which is partially bound to proteins and hence only filtered in part, plasma phosphorus is filtered almost completely and enters the tubular fluid in approximately the same concentrations as those present in plasma .

As with the general population, people with CKD have baseline risks for bone disease that increase with loss of kidney function. Generally speaking, since bone is a contributor to phosphorus homeostasis, the prevalence- of bone disease in U.S. adults should be taken into account when considering patients with CKD. More than 10 million U.S.

Adults over age 50 have osteoporosis, a preventable bone disease[46] . Furthermore, it is estimated that more than 33.6 million adults over age 50 have reduced bone mass .Recent reports indicate that approximately 14% of U.S. adults have CKD, and 33% of U.S. adults aged 60 and older have CKD, approximately 15 million people. Therefore, a majority of these patients will have osteopenia or osteoporosis in addition to the mineral-bone disorder of CKD.

Females aged 13 years and older meet the recommended amount of dietary calcium from foods, and even with dietary supplements, fewer than half of men aged 50 and older get an adequate amount of calcium.

In addition, dietary vitamin D intake is inadequate in the majority of adults even when accounting for dietary supplement use[49] .This is important for bone health as well as cardiovascular and kidney health because biomarkers of bone turnover (e.g., serum parathyroid hormone, urine excretion of N-terminal telopeptide of type 1 collagen) are increased and biomarkers of bone formation (e.g., bone-specific alkaline phosphatase) are decreased when dietary phosphorus intake is proportionally higher than dietary calcium intake.

Increased bone turnover releases calcium and phosphorus into the circulation, leading to vascular medial calcinosis and a compensatory increase in parathyroid hormone and the phosphaturic hormone FGF23 to handle the increased phosphorus load[50,51] .

Ultimately, bones are potentially weakened and excess calcium is deposited into soft tissues because dietary nutrient intakes are inadequate (e.g., < 1000 mg/d of calcium) or excessive (e.g., > 700 mg/d of phosphorus). As kidney disease progresses and there is less ability to balance phosphorus through urinary excretion, the increased circulating phosphorus further exacerbates bone turnover. By Stage 4 CKD, it becomes apparent that circulating phosphorus is increasing, and by Stage 5 CKD, serum iP control requires the use of phosphate binder medications in addition to chronic dialysis.

CHAPTER THREE

CONCLUSIONS

Conclusion

Phosphorus in the body is in the form of phosphate, serum phosphate is present in two forms organic and inorganic .organic phosphorus is composed entirely of phospholipid bound proteins .Inorganic phosphorus is the form that is measured and used[52] . Most of the body's inorganic phosphorus is intracellular and combined with calcium within the skeleton; however ,approximately 15% of the phosphorus exists in the blood as a phosphate salt[53] .

In Chronic Kidney Disease (CKD) the kidneys fail to excrete the phosphorus and the result is a positive phosphorus balance. However, the skeleton through the disorders of the bone that accompany CKD, contributes to this hyperphosphatemic state as it can not handle the phosphorus excess. So, in this new situation there is a need for a new phosphorus reservoir and this is soft tissue organs including vasculature[23,54] .The final result is vascular calcification that is frequently observed in CKD[54,55] . Experimental data have shown that phosphorus is involved in the whole process of vascular calcification leading to a new consensus that has renamed the old term of renal osteodystrophy with CKD mineral bone disorder (CKDMBD) and emphasizes the almost neglected role of the skeleton in these pathological states.[23,55,56] .

Phosphate overload and hyperphosphatemia have emerged as risk factors for vascular calcification, cardiovascular mortality, left ventricular hypertrophy and progression of chronic kidney disease. Normoprotein or high-protein diet may increase uremic symptoms and hyperphosphatemia, Even relatively small elevations of serum phosphorus in the high normal range have been correlated in observational studies with increased cardiovascular and all cause mortality in patients with CKD, diabetes, coronary artery disease, or even normal adults. Phosphate load may be an important driver of vascular calcification, even in the absence of overt hyperphospahatemia.

But low protein intake and increased mortality in dialysis patients suggests that alternative methods are needed to reduce phosphorus absorption. diet with a too low-protein content can favor malnutrition and increase morbidity and mortality . However a low-protein diet can slow the progression of renal disease[36] .

Current recommendations from various authorities suggest that serum phosphorus levels should be maintained between 2.7- 4.7 mg/dl in patients with CKD 3-4 and 3,5-5,5 mg/dl in CKD 5 via dietary phosphorus restriction or therapy with phosphate binders(23,57).
Although previous studies have shown a beneficial effect of a low in phosphorus diet, recent data indicate that this approach is frequently accompanied by an excessive risk of malnutrition and should be avoided[58].

The studies regarding therapies with phosphate binders have mainly focused in dialysis patients and there are only a few studies with a limited number of patients in CKD 3-4 patients with sevelamer hydrochloride[59], sevelamer carbonate[60] of lanthanum carbonate[61].

Furthermore, protecting and monitoring bone health should also aid in controlling serum phosphorus as CKD advances.

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