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CHRONIC KIDNEY DISEASE-MINERAL BONE DISORDER IN DIABETES MELLITUS PATIENTS

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Abstract

Diabetes mellitus (DM) and chronic kidney disease (CKD) are two diseases with increasing prevalence and adverse outcomes that represent an international health problem. Chronic kidney disease- mineral and bone disorder (CKD-MBD) is defined as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength and vascular or other soft-tissue calcification. Disturbances in mineral and bone metabolism are prevalent in CKD and are an important cause of decreased quality of life, cardiovascular morbidity and mortality; these disturbances settle in earlier and have a more severe evolution in DM patients.

key words: *chronic kidney disease, chronic kidney disease-mineral and bone disorder, diabetes mellitus*

Introduction

Chronic kidney disease (CKD) is a worldwide health problem affecting 12-13% of the United States' population [1]. Despite growing concerns of the medical community, the number of CKD pacients remains still unknown and estimations might underestimate the global burden [2-4]. Currently it is believed that 1 in 10 Romanians is affected by this disease and 10,500 benefit from renal replacement therapy (RRT) in hemodialysis (HD), continuous ambulatory peritoneal dialysis and renal transplant, with a growth rate of 8% over the previous year, the increasing prevalence of RRT in Dolj was no less than 26.4% [5].

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CKD contributes to almost 10% of deaths from any cause, a rate comparable to that caused by obesity and smoking [4], and current medical data reveal an indisputable fact: the survival of patients with CKD is dramatically influenced by cardiovascular pathology [2, 3, 6]; the leading cause of mortality in patients with CKD and in dialysis patients is cardiovascular disease [1-7] while up to 45% of patients with CKD die before initiating RRT [7].

Urbanization, increasing obesity, sedentarism, changing lifestyles and changes in population demographics have contributed together to a dramatic increase in the global incidence and prevalence of diabetes mellitus. The global burden of diabetes has reached dramatic proportions, each years' estimations underrate the real numbers; curently we know that, worldwide, 366 million people have diabetes (overexceeding the old estimations for 2025), 50% of which are unaware of their condition. It is estimated that by 2030 the number of patients suffering from diabetes will have risen to 552 million [8, 9].

Type 2 diabetes is by far the most common form of diabetes and accounts for 90–95% of the diagnosed cases; it is usually associated with older age, sedentarism, obesity, personal history of gestational diabetes or family history of type 2 diabetes [10].

Diabetes is the leading cause of kidney failure, accounting for 44% of the new cases in 2005 in the US [10], 29.3% of the Austrian incident RRT pacients have as primary renal disease diabetes mellitus [11] and the Romanian Renal Registry reports 13.3% of the incident RRT cases as being related to diabetic nephropathy [5] but the number of CKD patients with diabetes is much higher going up to 30-40%.

Taking into consideration the burden of the 2 diseases and the intricating complications we have proposed to briefly summarize the mineral and bone disorders induced by CKD in diabetic patients.

Chronic Kidney Disease – Mineral Bone Disorder (CKD-MBD)

CKD-MBD is the new term introduced since 2006 and that, in 2009, made the subject of a guideline edited by „Kidney Disease: Improving Global Outcomes" (KDIGO) in order to replace the old term of renal osteodistrophy that did not cover the whole complex interplay between *Ca, P, iPTH and Vitamin D metabolism, abnormalities of bone turnover, mineralization, volume, linear growth or strength* and *the vascular or other soft tissue calcification* [12]. These abnormalities set in early in the progression of CKD even before estimated glomerular filtration rate (eGFR) falls under 60ml/min/1,73m^2 and they continue to develop thus leading to secondary hyperparathyroidism as the renal function deteriorates.

The Bone

The bone, the organ that is the object of many changes induced by impaired renal function, is formed of collagen fibres mineralised by fixation of hydroxyapatite; in healthy individuals it is in a continuous process of remodelation with a balance between synthesis and resorbtion in order to regulate calcium homeostasis, repair micro-damaged bones and also shape and sculpture the skeleton.

Bone's metabolic functions are extremely important in the pathogenesis of CKD-MBD in diabetic patients because it acts as a *mineral*

reservoir (most notably for calcium and phosphorus), *growth factor storage* (insulin-like growth factors etc), *fat storage*, *acid-base balance* (absorbes/releases alkaline salts and thus buffers against *p*H changes), *detoxification* (stores heavy metals thus removing them from the blood and reducing their effects on other tissues, i.e.: aluminium deposits in the past, at the begining of HD), *endocrine organ* (secretes fibroblast growth factor-23 (FGF-23) - which acts on kidneys to reduce phosphate reabsorption [13], and osteocalcin - which contributes to the regulation of blood sugar (glucose) and visceral fat deposition; it also increases insulin's secretion and sensitivity, in addition to boosting the number of insulin-producing cells and reducing stores of visceral fat [14].

In CKD-MBD we can find several types of skeletal lesion: *high turnover* (high PTH, hyperactive bone cells and excess bone resorption), *low turnover* (adynamic bone with little or no bone activity and normal or low PTH), *mixed lesions* (features of both of the above with no PTH correlation), *osteoporosis* (most frequent in elderly, diabetic patients or due to corticotherapy) and *osteomalacia* (generated by aluminium deposits or vitamin D deficiency) [12].

Phosphorus

Phosphorus (P) seems to be the main agent in CKD-MBD because its levels trigger the vicious circle and all the other factors involved in this condition regulate according to it. The damaged kidney is unable to excrete all the phosphorus load and it starts to accumulate early in CKD stage 2, with eGFR<70ml/min/1.73m^2 [15]. Hyperphosphatemia (seric P>4.6mg/dl) is one of the first abnormalities that settle and it leads to the inhibition of 1-α-hydroxylase and further on to the imposibility of converting vitamin D into calcitriol, its active metabolite. Hyperphosphatemia stimulates PTH production and high level of P has been associated to vascular calcification [16, 17], decline in renal function [18] and it is also an independent cardiovascular risk factor in CKD [19].

Although hypophosphatemia is usually seen in conjunction with diabetes mellitus due to the excessive phosphorus loss in urine, the seric phosphorus can be high because of metabolic acidosis and insulin deficiency (or severe hyperglycemia alone) that can cause a shift of intracellular phosphate into the extracellular milieu [20, 21, 22].

Calcium

Calcium (Ca), the 5th-most-abundant element by mass in the human body is a common cellular ion, but also serves as a structural element in bone where, together with phosphorus, forms hydroxyapatite.

In healthy individuals, serum calcium is within 8.5-10.5mg/dl but in CKD patients hypocalcemia is often found especially when eGFR falls under 20ml/min/1.73m^2. Hypocalcemia induces PTH secretion whereas hypercalcemia inhibits PTH secretion. In return, PTH stimulates osteoclasts activity and, by its effects on active vitamin D, intestinal Ca uptake; thus elevating circulating Ca levels [12, 15, 23].

Calcium is strongly related to phosporus and often we take into consideration CaXP values and not Ca or P alone in order to establish mineral disorders in CKD patients. In dialysed patients, this product should be <55mg^2/dl^2 and values higher than this correlate with vascular calcification score and mitral valve calcification [17, 23].

Until recently, for more than 20 years, calcium has interested doctors more for its properties of binding intestinal phosphorus, therefore calcium-containing phosphorus binders have been largely used. More recently, concernes regarding the use of calcium-based dietary phosphorus binders have risen as, on the long run, they promote vascular calcification and by thus increase cardiovascular morbidity and mortality in CKD patients [17].

Vitamin D correction could be amongst the answers as it could lead to better protection against hypocalcemia and thus reducing secondary hyperparathyroidism's effects but this does not resolve the problem of phosphate binders.

Moreover, calcium, vitamin D, or dairy intake appear to be protective factors against type-2 diabetes and metabolic syndrome by improving blood sugar and insulin levels as it appears in a meta-analysis and review conducted by Pittas AG. "Evidence from trials with vitamin D and/or calcium supplementation suggests that combined vitamin D and calcium supplementation may have a role in the prevention of type-2 diabetes only in populations at high risk (i.e. glucose intolerance)" said the author [24].

Vitamin D

Vitamin D is a prehormone obtained through diet (10-20%) or via skin synthesis (exposure to UVB converts 7-dehydrocholesterol to cholecalciferol - vitamin D3). Further on, vitamin D, whether from skin or diet is subsequently activated in a 2-step process, the first one takes place in the liver and it involves 25-hydroxylation to produce 25(OH)vitamin D and then 1-α-hydroxylation which occurs primarily in the kidney, to produce the active metabolite: 1,25$(OH)_2$vitamin D or calcitriol. But a small quantity of calcitriol is also formed through an alternative pathway as 1-α-hydroxylation can take place in many other organs such as lung, colon, breast or prostate. Optimal serum levels of 25-(OH)vitamin D should be 40-80 ng/mL [25].

Hypovitaminosis D has high prevalence in general population but patients with CKD are affected to a greater extent and its consequences are more severe. Although the mecanisms are not fully understood, proteinuria (renal loss of vitamin D binding protein) could be responsible for this. We must also keep in mind micro and macroalbuminuria in diabetic nephropathy as a possible pathogenic pathway for vitamin D deficiency [26, 27].

Low vitamin D levels lead to low intestinal calcium uptake, hypocalcemia and it increases PTH secretion; the subsequent secondary hyperparathyroidism represent a mortality risk factor for this populational group [2, 3].

Vitamin D treatment, although proven to reduce cardiovascular morbidity and mortality, can lead to hypercalcemia and hyperphospatemia which are correlated to vascular calcifications [28] so the treatment shoudn't be conducted without vitamin D, Ca, P, PTH seric value periodic evaluation.

Although it is known that vitamin D plays an indirect role in arterial stiffness, high blood pressure, vascular calcification and heart disease, a recent meta-analysis stated that vitamin D is not an independent cardiovascular risk factor [29].

In addition to calcitriol's pleiotropic effets, paricalcitol- a vitamin D analogue, has been associated to further more downregulation of PTH, inhibition of rennin

synthesis (the inhibition of renine-angiotensine system is a proven way to prevent/slow the progression of diabetic nephropaty), reduction of proteinuria, inflammation, atherosclerosis and vascular calcification [29, 30].

Parathyroid hormone and fibroblast growth factor 23

Renal phosphate excretion is regulated mainly by the parathyroid hormone (PTH) and by FGF-23. In healthy individuals, high serum phosphate levels induces PTH and FGF-23 secretion and these two phosphaturic hormones reduce phosphate reabsorption and increase urinary phosphate excretion [19, 31].

PTH is a peptide hormone that is secreted by the chief cells of the parathyroid glands; it is involved in systemic calcium homeostasis, with bone and kidney as main target organs. On bone, PTH has a dual effect: increased secretion increases both number and activity of osteoblasts (anabolic effect) and osteoclasts (thus increasing bone resorption). Increased PTH levels increase intracellular calcium levels. In CKD-MBD each element involved in the process influences and is influenced by all the others. Thus, PTH increases the 1α-hydroxylase in the kidney, thereby increasing calcitriol production which enhances intestinal Ca and P absorption [32], but it also induces FGF-23 expression and secretion which, in turn decreases $1,25(OH)_2$ vitamin D production, which is an inhibitor of PTH production [31].

It could be concluded that PTH secretion is controled directly by ionized Ca, Vitamin D, P and Mg levels: hypocalcemia and hyperphosphatemia stimulates whereas hypercalcemia, vitamin D and severe hypomagnesemia inhibit. Acidosis, a condition to which both diabetic and renal patients are predisposed, occurs because of renal reduced bicarbonate reabsorption, stimulates osteoclast activity and PTH production and therefore treatment with sodium bicarbonate can reduce PTH levels up to 20% [33]. Apart from its implications in vascular calcification (PTH promotes Ca release from the bones and its deposition in smooth muscular cells), secondary hyperparathyroidism is an independent risk factor for cardiovascular mortality [34].

FGF-23 is a new player amongst the traditional factors (PTH and Vitamin D) that generate CKD-MBD; it is a hormon secreted in the bone, by osteocytes, and its main function is to increase phosphaturia, thereby restoring normophosphatemia. However, it also reduces active Vitamin D levels, thus contributing to an increase in PTH secretion. On the other hand, reduced serum levels of FGF-23 increase serum calcitriol and renal Klotho expression [35, 36, 37].

Mild decline of renal function leads to kidney's decresed capacity of excreting high phosphorus loads which determine FGF-23 levels to rise. By increasing PTH secretion, rising FGF-23 levels contribute to the development of secondary hyperparathyro-idism and may also be associated to alterations in skeletal mineralization in the CKD population [37, 38].

Recent data suggest that leptin directly stimulates FGF23 expression in bone [39]. FGF23 was also associated with dyslipidemia, 8% to 12% higher insulin and Homeostatic Model Assessment (HOMA) index, higher Body Mass Index (BMI), larger abdominal circumference, elevated triglycerides, lower HDL cholesterol; however, FGF 23 has not yet been independently associated with

diabetes mellitus [40]. Nevertheless, FGF-23 was demonstrated to be a significant independent predictor of renal outcome in patients with macroalbuminuric diabetic nephropathy [41, 42].

Klotho

Klotho, „the eternal youth gene" named after the ancient Greek goddess of fate was discoverd in 1997 and has recently been related to CKD-MBD; its deficiency may be the initial biomarker of CKD and the initiator of CKD-MBD.

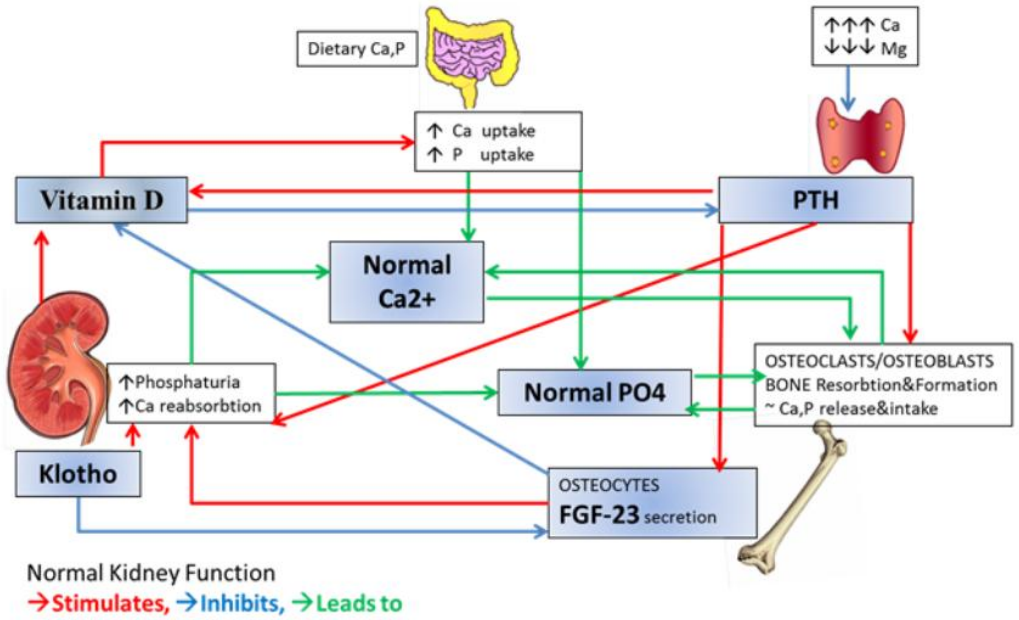

Figure 1. Regulation and effects of Ca, P, Vitamin D, Klotho, FGF-23, PTH in patients with normal kidney function.

Its actions are very complex; in the kidney, Klotho mediates phosphate excretion and feedbacks inhibition of calcitriol synthesis in response to FGF-23. In mice, Klotho deficiency causes hyperphosphatemia and accelerated aging phenotypes such as osteoporosis and arteriosclerosis. The decline of Klotho's expression begins early in CKD and it may precede both high P and FGF-23 seric levels, yet further research is needed in order to establish which is the first to initiate this vicious cercle (Figure 1 and Figure 2). This discovery is very important as it is thought that maintaining normal phosphatemia with phosphate binders in patients with CKD with declining Klotho expression can prevent or even reduce mineral and vascular derangements [42, 43].

Decrease of Klotho expression induces an increase of FGF-23 which is responsable for lowering circulating calcitriol, further depressing Klotho expression and increasing PTH. PTH stimulates further FGF-23 increases, causing large decreases in active vitamin D and large increases in PTH. The result of this cycle is hyperphosphatemia in late stages of CKD.

Cheng et al. reported reduced Klotho expression under hyperglycemic condition in kidney and they concluded that decrease of Klotho expression is related to the process of diabetic nephropathy [44]. Dr Kuro-o who first discoverd Klotho strongly belives in its potential: "Klotho proteins thus will be important players in future therapies for human conditions such as diabetes, obesity and kidney disease."

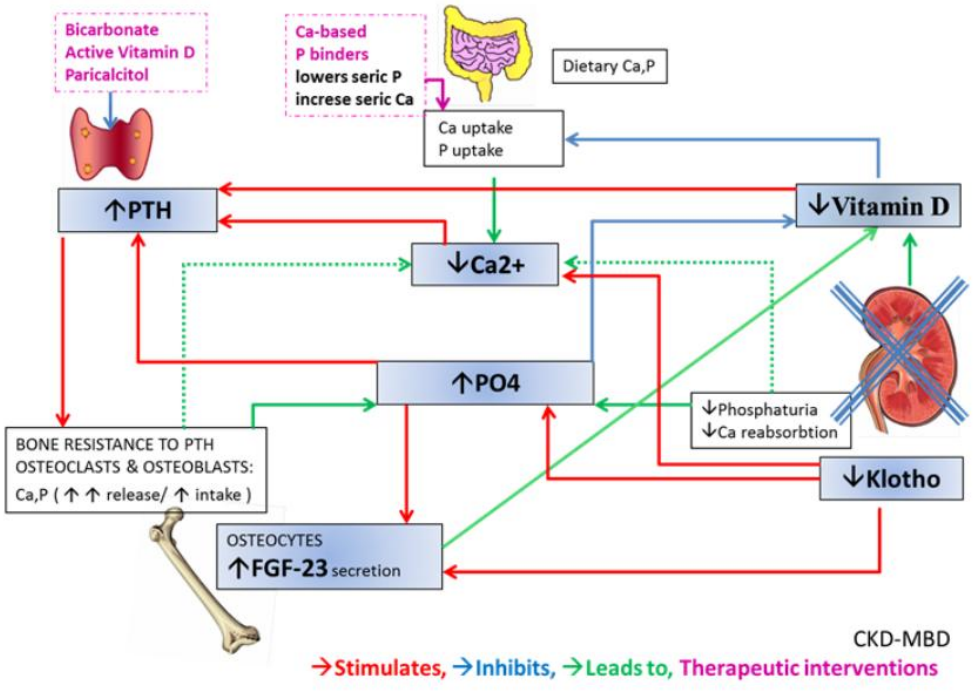

Figure 2. Summary of the factors which predominate in CKD-MBD; their regulation and therapeutic suggestions.

Vascular calcification

Although vascular and valvular calcifications are not unusual in the general population, they are more common in the elderly as well as in CKD patients. It is now known that more than 90% of atherosclerotique plaques are calcified in the elderly [45] and aortic calcification affects 20-30% of people aged over 65 years old [46].

There are 2 types of vascular calcification according to the vascular layer in which the process occurs: intimal and medial calcification.

Intimal calcification is the hallmark of atherosclerotic disease, it is found in general population as well as in CKD and dialysed patients and it develops on an atherosclerotique plaque. It narrows further more the vessel lumen and it is associated with stroke, angina and myocardic infarctus.

‚Medial calcification', ‚arteriosclerosis' or ‚Monckeberg's calcific sclerosis' – as the second type of vascular calcification is also known, refers to the calcification of the tunica media without thickening of the intima or reducing of the vascular lumen. It is rather specific in diabetic patients and in CKD patients. Medial calcification affects distal vessels, it can co-exist with intimal calcification and it determines arterial stiffness, left ventricular hypertrophy and reduced coronary perfussion [16, 47].

Vascular calcification increase cardiovascular risk but it is difficult to say which type of vascular calcification is of worst prognosis as they most often cohabitate. Moreover, we can also find valvular calcifications, most often involving the mitral valve in HD patients, this also associates with higher mortality risk [48].

The pathogenesis of ectopic ossification occuring in the smooth muscular cells is very complex and it has not been yet explored to a level that gives complete understanding; nevertheless it is known that inflammation, uremia, PTH, Ca, P, osteonectin, hyperhomocysteinemia, osteopontin play

important roles [12]. What is beyond any doubt is the fact that vascular calcification is an important cardiovascular risk factor and that this process is accelerated in CKD patients, especially in the stage 5D of the disease [2, 3, 6, 16, 17, 23, 45, 46, 48].

Conclusions

CKD-MBD deals with mineral and bone abnormalities that set early in the progression of CKD even before eGFR falls under 60ml/min/1,73m2 and they continue to develop towards secondary hyperpharathyroidism as the renal function deteriorates. Diabetic patients are at risk of developping earlier and more severe manifestations of this condition but the extent of all these has not yet been established [49]. Further research is needed in order to identify specific biomarkers and efficient therapies that could prevent the initiation and/or progression of these complications.

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