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Review Article

Acid-base disorders and the impact on metabolic bone disease in hemodialysis patients

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Abstract

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is a term that is used to describe a wider clinical syndrome that can be developed as a systemic metabolic mineral bone disturbance, due to the chronic kidney disease, and it manifests itself as metabolic mineral bone anomalies or extra-skeletal calcifications. Metabolic acidosis is considered to be the most widespread acid-base disorder that is found in the majority of CKD patients. Hemodialysis patients seem to be more prone to MBD due to acid base disorders. This article aims to review the available literature about the acid-base disorders and their impact on MBD in hemodialysis patients. We have conducted an electronic literature research, where titles and abstracts of relevant papers were validated by the authors for further inclusion in this work. Finally, full texts of the included articles were retrieved. The findings of our literature research have concluded that at the age of 55, the relative risk of hip fractures increases and in CKD patients is high; after 4 years of undergoing dialysis, the age-specific relative risk of suffering a hip fracture was 9.83 for males and 8.10 for females. The average relative risk of mortality associated with hip fracture was 1.99. Our review has highlighted that CKD and MBD are closely related and they consist of a phenomenon requiring further research.

Keywords: Chronic Kidney Disease, Hemodialysis, Metabolic acidosis, Mineral Bone Disorder

Introduction

The kidney constitutes a vital organ in the human body, with multiple roles[1]. The kidney metabolizes the minerals and assists in bone health; the kidney is considered to be the main organ of various hormones that operate as regulators, for example parathormone (PTH) and fibroblast growth factor-23 (FGF-23). Also, the kidney is the primary organ that activates Vitamin D[2,3].

Chronic kidney disease is thought to be a global health problem affecting approximately 10% of the global population[4]. The larger part of CKD patients run the risk of suffering from metabolic mineral bone disturbances. These metabolic mineral bone disturbances cause a sequence of bone lesions, previously named as Renal Osteodystrophy (RO); the patients affected by these disturbances manifest various symptoms, namely bone pain, pruritus, muscle-tendon rupture, and frequent occurrence of fractures[5,6].

We use the term Chronic Kidney Disease- Mineral and Bone Disorder (CKD-MBD) to describe a wider clinical syndrome that is developed as a systemic metabolic mineral bone disturbance, as a result of the chronic kidney

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disease, and it manifests itself as metabolic mineral bone anomalies or extra-skeletal calcifications[7]. CKD-MBD is better defined as "a systemic metabolic mineral bone disorder resulting from CKD, with either one or multiple of the following symptoms: *a) metabolic abnormalities of PTH, calcium, phosphorus, or Vitamin D; b) abnormalities concerning bone turnover, bone volume, mineralization, linear growth or strength; c) vascular or other soft tissue calcification*"[8]. This definition has been globally accepted and it has helped bring about valid comparisons between studies concerning CKD-MBD[9].

Distinguishing between kidney osteodystrophy and osteoporosis, as it is identified in the general public, is indiscernible, due to the fact that both diseases share causality and pathogenic factors with a shared range of biochemical and histological abnormalities[10].

For patients with CKD stage I to III, any abnormalities that are categorized in the CKD-MBC syndrome, such as secondary hyperparathyroidism (HPT) and hyperphosphatemia, are quite mild, if manifested. Thus, for these patients, osteoporosis probably does not result from CKD and it can be classified as a typical osteoporosis (postmenopausal, aging osteoporosis or medication-induced). For patients, however, with advanced CKD, stage IV to V, the role CKD-MBD syndrome plays is crucial and the medication treatment differs[11]. Also, metabolic acidosis can be characterized as a common complication of CKD, especially through its end stage[12]. Renal insufficiency can affect all parameters involved in the renal excretion of excess acids from the body, when Glomerular Filtration Rate (GFR) is reduced to levels below 40-50 ml/min, the remaining kidneys are unable to maintain their ability to excrete daily acid load. Further deterioration of renal function at GFR levels<15 ml/min results in metabolic acidosis occurring in the majority of patients (pH<7.3, HCO_3^-=12-18 mEq/L). Increasing the concentration of hydrocarbons would lead to a further reduction in the concentration of bicarbonate, which is avoided due to the neutralization of excess H^+ by regulatory systems of the body and especially the bones. Bicarbonate treatment protects patients from the risk of developing osteopenia, a complication of metabolic acidosis in patients with CKD[13-15].

Literature search method

Using the MEDLINE/PubMed database, we searched keywords such as "Chronic Kidney Disease (CKD)", "Mineral Bone Disease (CKD-MBD)", "Hemodialysis" and "Acid-Base Balance". We searched for relevant and appropriate information from all the references that were identified in the articles. Our literature search ended in July 2020 and its main focus was on the most recent published information concerning the effects of acid-base disorders in the metabolic bone disease in hemodialysis patients.

Pathogenesis of CKD-MBD

Role of FGF-23

A reduced phosphorus secretion in CKD leads to increased FGF-23 production; the molar concentration of FGF-23 is also increased due to its retention and its secretion deficiency, as a consequence of kidney failure. FGF-23 increase is a sign of early stages of CKD; its usage can be a predictive indicator of this disease, according to what has been suggested in the literature. During the early stages of CKD, phosphorus levels are stable through the increase of FGF-23, to the expense of the reduced repression of parathyroid glads and the manifestation of secondary hyperparathyroidism. In more advanced stages, where failure of kidney function cannot secret excess phosphorus, an increased amount of FGF-23 assists in developing secondary hyperparathyroidism. In the final stages of CKD, FGF-23 shows a positive connection to cardiovascular incidents and is considered as a predictive risk indicator. For patients undertaking peritoneal dialysis, FGF-23 molar concentration shows a positive connection to the left ventricular hypertrophy[2,16,17].

Role of Klotho

Klotho is known to be a transmembrane protein transmitting tissue specificity to FGF-23. This co-receptor and its significance was depicted in klotho null lab mice, depicting a similar phenotype of FGF-23 null lab mice, showing features of premature aging, metabolic alteration of calcium-phosphate with hyperphosphatemia, vascular calcification and a shortened lifespan. According to studies, a disarranged FGF23-Klotho axis, defined by a low level of klotho serum and at the same time, high level of FGF-23, is a feature of the early stage of CKD. It is known that klotho has a cardinal role in mineral homeostasis, as it interacts with alternative CKD-MBD markers (parathyroid hormone, fibroblast growth factor-23, phosphate and 1.25-[OH]-2 Vit. D3[18].

Evidence from hemodialysis patients has shown the loss of FGF-23 ability to adjust phosphate into normal levels by its phosphaturic action and to balance PTH secretion, showing elevated levels of FGF-23, related to the elevated levels of PTH. The uncoordinated compensatory mechanism of FGF-23 has been widely associated to klotho deficiency in CKD, which can be characterized by low expression of klotho and FGF-23 receptor 1 in the parathyroid gland. Klotho is the main component in the conversion process of FGFR1(IIc) into a specified receptor for FGF-23. Klotho is also known as a calciophosphoregulatory protein, since it enhances phosphaturia and prevents calcium loss. Therefore, klotho deficiency may bring about a sequence of uncoordinated mineral metabolism, vascular calcification, secondary hyperparathyroidism and cardiac hypertrophy; an exogenous administration of klotho could alleviate the development of CKD-MBD[18,19].

The impact of metabolic acidosis on bone regulatory hormones

A significant amount of data has been collected regarding how metabolic acidosis affects the bone, suggesting that it may modify the secretion process of bone regulatory hormones, for instance PTH and Vitamin D. Hormone PTH augments bone absorption by increasing the secretion pace of protons and degradative enzymes by osteoclasts and it is vital in bone remodeling process[20]. As mentioned in the literature, an oversupply of PTH secretion usually leads to the amelioration of chronic renal failure, concluding in developing hyperparathyroid bone disease. The effect of metabolic acidosis which are induced in vivo in humans and animals with normal renal function for the serum levels of PTH has been examined in the literature[21].

The results of the observation in circulating PTH levels have shown an increase, no change or even a decrease. The cause for the discrepancy in the results cannot be clearly identified, but maybe related to discrepancies concerning the levels of divalent ions or how severe the metabolic acidosis has been noted in various studies[22,23]. Though a notable increase in serum levels of PTH does not take place simultaneously with metabolic acidosis, PTH action in the bones seems to render larger by metabolic acidosis. It has been claimed by Beck and Webster that the calcemic response to PTH in rats was increased when metabolic acidosis is present. Martin et al have developed an effective mechanism for this effect of calcemic response, with the use of an isolated perfused bone preparation[3,9,24].

Martin et al. (2007) have pointed out that when simulating an acute metabolic acidosis in vitro, the PTH intake and the cyclic adenosine monophosphate that bone cells produce is increased. Since PTH plays a presumed role in stimulating osteoclast action, a logical assumption would be that it also plays a role in buffering an acid load by the bones. Nonetheless, the role of PTH in buffering an acid load is a controversial issue; some studies have shown that a rise in PTH levels was critical to the above mentioned buffering process, while other studies has concluded that it plays little or no role in it[3,25,26]. Vitamin D constitutes in metabolizing divalent ion by inducing a stimulation of calcium and phosphorus intake by the gastrointestinal track and probably by affecting the bone directly. Undeniably, reduced serum concentrations of 1,25-Hydroxy Vitamin D, which is the active metabolite of Vit. D, have been pointed out by researchers in the pathogenesis of bone disease of metabolic acidosis[20,27]. It has been claimed by researchers studying the effect of an acidic milieu on converting 25-hydroxy Vitamin D to the active metabolite or the action of the enzyme I-a-hydroxylase in renal tubules or tissues that there is a decrease of the enzyme or the production of 1,25 D with short-term acidemia (hours to days)[25,28].

Cunningham et al. (1984), though, have claimed that when acidosis occurs continuously for more than three weeks, there is no indication for I-a hydroxylase activity[29]. There has been an inconsistency to the results of the basal serum 1,25 Vitamin D measurements and the results collected after stimulating with PTH infusion in both humans and animals showing metabolic acidosis and normal renal function. Serums levels of 1,25 Vitamin O have shown to be lowered, stable or even increased, as has been reported with PTH[30,31]. The alterations in the impact the metabolic acidosis shows to serum 1,25-Vit. D levels have been associated with various metabolic acidosis stages and the various serum phosphate levels that have been shown in studies.

In spite of the above mentioned, throughout most of the studies conducted in people and animals with typical renal function, it is evident that there is not an important reduction in serum 1,25-Vit. D levels concerning metabolic acidosis. Throughout a study, the 1,25-Vit. D levels were calculated in lab rats with renal failure that were administered hydrochloric acid in order to produce metabolic acidosis and non-acidotic uremic controls; there was no significant difference in 1,25-Vit. D levels throughout these groups[32,33].

Consequently, even though there is an implication of an altered Vit. D metabolism in the pathogenesis of MBD associated with metabolic acidosis, an irregular Vit. D metabolism is doubtful to be depicted as the main factor. The existing possible mechanisms through which metabolic acidosis may be partly responsible for involving: i) hydrogen intake in exchange for bone surface potassium or sodium, ii) dissolution of bone calcium carbonate, iii) a undeviating stimulation of osteoclast-mediated mineral dissolution, iv) prohibition of the function of osteoblact, v) stimulating the PTH secretion, vi) augmenting PTH, and vii) a dissolution of Vitamin D synthesis[34].

Metabolic acidosis and MBD

Metabolic acidosis is the most frequent acid-base disorder found in most CKD patients, when the GFR is less than 20-25%, contrary to the normal values. A metabolic acidosis could be activated by the following three mechanisms:

a. Increasing the generation acid
b. Loss of bicarbonate
c. Decreased excretion of renal acid

When concerning patients in the end-stage renal disease, the mechanism that is involved is the diminished renal excretion of hydrogen ions[35]. The factors which usually promote metabolic acidosis worsening in hemodialysis are: a lower gaining of bicarbonate in dialysis which is due to inadequate levels of bicarbonate in the dialysate, inappropriate dialysis program or non-attendance of it, an intake which is high in proteins or bicarbonate loss through the gastrointestinal tract[14,36].

Usually, the acidosis is mild to moderate and the bicarbonate concentrations range from 12 to 22 mEq/L (mmol/L). The level of the acidosis corresponds with how severe the renal failure is. The lower the GFR, the more severe the metabolic acidosis is depicted and this is the cause for many diseases, namely muscle wasting, impaired

growth, progression of renal failure, abnormalities in the growth hormone and in how the thyroid hormone is secreted, accumulation of β2-microglobulin, impaired insulin sensitivity and bone disease[34].

Due to the presence of metabolic acidosis, changes in the bone mineral composition take place which are responsible for reducing sodium and potassium bone, reduction of bone carbonate and increased serum calcium[37]. Moreover, increased presence of calcium in the urine without an increase on intestinal calcium at the same time, reveals that the excreted calcium is supplied by the bone[38].

Studies on the effects of MBD on hemodialysis patients

Despite the fact that a great progress has been done to understand bone disease in CKD and hemodialysis patients, the process of managing fragile bones remains inadequate. Supplementing Vitamin D and achieving serum levels of 25-hydroxyvitamin D are used in patients with CKD in order to decrease high levels of parathyroid hormone associated with skeletal fractures. Controlling the parathyroid hormone helps to lower the levels of cross-linked collagen type I peptide and of alkaline phosphatase and thus improving bone mineralization.

The Kidney Disease Improving Global Outcomes guidelines published in 2009, as in the 2017 revised version, have included recommendations about the evaluation and the treatment of biochemical, cardiovascular abnormalities and bone abnormalities. Except from the introductory criteria that shows the existence of metabolic bone disease, which are based on bone biopsies, bone volume and mineralization, alternative bone markers of fragility are added[17].

At the age of 55, the relative risk of suffering hip fractures increases and in CKD patients is high. Also the mortality risk after suffering a hip fracture in CKD patients is elevated too[6,39,40]. Alem et al. (2000) revealed that the total relative risk for hip fracture existing in dialysis patients was 4.44 for males and 4.40 for females, while the age specific relative risk (ASRR) of suffering a hip fracture was highest in younger age groups. Specifically, after 4 years of dialysis, the ASRR was 9.83 (95%CI, 8.61-11.2) for males and 8.10 (95%CI, 7.23-9.07) for females[41]. Moreover, another research from Nitsch et al. has showed that in older CKD patients, the hip fracture related mortality risk is 2 times higher when the eGFR is lower than 45 ml/min/1.73 m^2 [42].

Mittalhenkle et al. (2004) studied 7.636 dialysis patients who had a hip fracture throughout the study period, as compared to 22896 non-fractured dialysis patients. The average survival time when suffering a hip fracture was 289 days (95%CI, 275-302), whereas for the non-fractured patients was 714 days (95%CI,697-732); the average relative risk of mortality that is associated with a hip fracture was 1.99 (95% CI,1.91-2.07[43].

Gerakis et al. (2000) examined how BMD is distributed in various histological groups of RO in 62 hemodialysis patients[44]. They used bone biopsy after tetracycline labeling and dual-energy X-ray absorptiometry measurement at the proximal femur and lumbar spine. The findings were that 40 patients revealed secondary hyperparathyroidism, 14 adynamic bone disease, 6 mixed bone disease and 2 osteomalacia. Lumbar spine BMD was lowered in 43 patients, whereas in 9 it was <-2 Z score units. Femoral neck BDM was decreased in 55 patients, whereas in 22 it was <-2 Z score units. Patients with sHPT had lower BDM compared to patients with adynamic bone disease. They concluded that osteopenia in more frequent in hemodialysis patients, specifically in those with sHPT biochemical and histological findings[44].

Discussion

End-stage renal disease is connected to significant modifications in body fluids homeostasis, in acid-base equilibrium, in cardiovascular function, in electrolytes, in bone metabolism, erythropoiesis and blood coagulation. Undertaking a dialysis routinely can remove up to 70% of absorbed phosphorus. Thus, a hyperphosphatemia is a symptom found in most of the patients with ESRD. A consequence of this imbalance may be the appearance of secondary hyperparathyroidism and osteodystrophy[7,45].

Patients with CKD are characterized by carrying various conditions that may be considered as an indication to fracture. It has been calculated that the risk of suffering a fracture for CKD patients is analogous to people of the general public that belong to an age group of 10 to 20 years older than CKD patients. More specifically, to CKD patients at the IV stage, the consequences of having a fracture are multiplied four times. For patients undertaking dialysis, the relative risk is calculated more times more frequently comparing to the general public and it is increased during the dialysis procedure. As far as the statistics figures are concerned, the risk corresponds to a hip fracture or 2.6 more possibilities of having fractures to all anatomical positions per 100 years and it is approximately 2 times more frequent to women.

The mortality from hip fractures is more for the general public and even higher from kidney failure patients (61% during the first year comparing to 36% for the general public). When dialysis patients suffer from a hip fracture, they show a double mortality rate, as compared to other patients[6,7,41-44,46].

Conclusion

In this article, the present knowledge about the effects of acid - base disorders and especially of metabolic acidosis on metabolic bone disease in hemodialysis patients was reviewed. Bone strength disorders are usually generated by abnormalities of bone structure or bone mass, with osteoporosis being the most common disorder. Hemodialysis in CKD patients increases the risk of suffering bone failure and when untreated, osteoporosis can lead to bone deformities, fragility fractures, and ultimately, serious

disability. Few of the above effects were documented in studies, but further studies need to be done, in order to understand more the mechanism that provokes the MBD, as well as to find the effect of metabolic alkalosis in dialysis patients, as a consequence of acidosis overtreatment.

Authors' contributions

EE: Drafted the manuscript, reviewed literature. GIL: Proof-edited the manuscript and gave final permission for publication.

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