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The relation between serum calcium levels and acute kidney injury in ICU: an overview

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Abstract

In skeletal development, hemostasis, muscle and nerve function, cellular metabolism, and signal transduction pathways, calcium and phosphate are vital components of physiology. Kidney disease (KD) patients experience a significant disturbance in the metabolism of minerals and bone, leading to a complex condition known as KD-mineral bone disorder (KD-MBD). As kidney disease advances, disturbances start in the early stages of the condition and get worse. KD-MBD is characterized by biochemical changes such as increased levels of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23), decreased levels of 1,25-dihydroxyvitamin D (1,25D), elevated levels of blood phosphate, and decreased levels of serum calcium. One of the most frequent complications for hospitalized patients is acute kidney damage (AKI). Significantly, AKI has a separate correlation with both the advancement of chronic renal disease and in-hospital mortality. To lessen the severe clinical effects of AKI, early detection and treatment of the condition and its consequences are essential. AKI frequently results in a disturbance of calcium homeostasis. It is unclear, though, if calcium—more especially, corrected calcium—plays a part in the onset of AKI. For the previously mentioned facts, we performed this overview to formulate an idea about the relation between changes in serum calcium levels and acute kidney injury.

Keywords: Calcium; AKI; ICU; Kidney.

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1. Introduction

1.1 Aim of work

To determine the frequency and relation between hypocalcemia and ICU patients with acute kidney injury via serial assessment of serum total and corrected calcium, continuous evaluation of kidney functions and evaluation of the effect of hypocalcemia on clinical outcome of those patients.

1.2 Calcium and Kidney disease: golden keys

In skeletal development, hemostasis, muscle and nerve function, cellular metabolism, and signal transduction pathways, calcium is vital component of physiology. Less than 1% of the body's total stores are made up of circulating amounts of calcium; the bulk is stored in bones as hydroxyapatite, which can be released into the circulation in response to the body's metabolic needs. Three essential hormones work together to keep circulating calcium level in persons with normal kidney function within a certain physiological range: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25D), and fibroblast growth factor 23 (FGF23). The kidneys, bone, gut, and parathyroid glands are the main organs that these hormones target, while several off-target or nonclassical effects have also been found [1]. Kidney disease (KD) patients experience a significant disturbance in the metabolism of minerals and bone, leading to a complex condition known as KD-mineral bone disorder (KD-MBD). As kidney disease advances, disturbances start in the early stages of the condition and get worse. KD-MBD is characterised by biochemical changes such as increased

levels of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23), decreased levels of 1,25-dihydroxyvitamin D (1,25D), elevated levels of blood phosphate, and decreased levels of serum calcium [2]. Furthermore, there is evidence of excessive vascular and soft tissue calcification, as well as heterogeneous bone disease. Increased fracture risk, a higher frequency of cardiovascular events, and a higher death rate from cardiovascular causes are linked to KD-MBD [3]. One of the most frequent complications for hospitalised patients is acute kidney damage (AKI). Significantly, AKI has a separate correlation with both the advancement of chronic renal disease and in-hospital mortality. To lessen the severe clinical effects of AKI, early detection and treatment of the condition and its consequences are essential. AKI frequently results in a disturbance of calcium homeostasis. It is unclear, though, if calcium—more especially, ionised calcium—plays a part in the onset of AKI [4]. In patients with ARF, there is a decrease in the overall serum calcium concentration. The hypocalcemia of the oliguric phase may be caused by skeletal resistance to the calcemic action of PTH, hyperphosphatemia, and decreased availability of the active metabolite of vitamin D, 1.25 dihydroxycholecalciferol (DHCC). Acute tubular necrosis cases that are oliguric in nature and associated with rhabdomyolysis may exhibit hypercalcemia in the diuretic phase. This condition is caused by a number of mechanisms, including the mobilisation of calcium from injured muscles, deposits in soft tissue, secondary hyperparathyroidism that developed during the initial phase, and elevated levels of 1,25 dihydroxy vitamin D that developed during the initial phase as a corrective response to the hypocalcemia [1].

1.3 Mechanisms of hypocalcemia in AKI

Clinical studies of patients with developed AKI have repeatedly revealed low levels of circulating calcium. This discovery has been explained by a number of aetiologies. These include a decrease in the kidneys' ability to synthesise 1,25D, which lowers the amount of calcium that is absorbed from the stomach, the kidneys' ability to reabsorb calcium, and the bone's ability to release calcium [5]. Patients with AKI often have hyperphosphatemia, which can also lower total serum calcium levels by securing calcium in the bloodstream. When there is severe tissue breakdown (such as in tumour lysis syndrome and rhabdomyolysis), a significant amount of phosphate is abruptly released from intracellular reserves into the bloodstream. PTH and 1,25D, often known as calcitriol or "active vitamin D," are the two main hormones at play. The parathyroid gland's calcium-sensing receptors detect low serum ionised calcium, which triggers PTH production and secretion [6]. Furthermore, while AKI produces more PTH in response to hypocalcemia and low levels of circulating 1,25D, AKI's skeletal resistance to PTH reduces its procalcemic effects, which limits PTH's capacity to return serum calcium levels to normal [7]. The up-regulation of the calcium-sensing receptor (CaSR) in the kidneys and parathyroid glands, which happens in response to proinflammatory cytokines, is another possible explanation of hypocalcemia in AKI. The set point for the regulation of calcium-PTH feedback may be impacted by this CaSR up-regulation. Lastly, individuals with septic AKI may experience a buildup of intracellular calcium. To clarify the relative contributions of each of these possible pathways, more research is required [8]. Typically asymptomatic, the hypocalcemia linked to AKI doesn't need special care. Intravenous calcium is necessary for the treatment of symptomatic hypocalcemia; however, if concomitant severe hyperphosphatemia is present, the aggressiveness of therapy may need to be moderated to avoid the risk of metastatic calcium phosphate deposition from calcium infusion [9].

1.4 Clinical relevance of hypocalcemia in AKI

Adverse effects on the cardiovascular system, including both hemodynamic and arrhythmogenic consequences, are among the several clinical manifestations of hypocalcemia that are most pertinent to outcomes related to AKI. In particular, patients with hypocalcemia may have hypotension due to a decrease in cardiac contractility or systemic vascular resistance [10]. Additionally, QT interval prolongation brought on by hypocalcemia raises the possibility of polymorphic ventricular tachycardia, or Torsades de pointes. However, in clinical reality, hypocalcemia-related Torsades de Pointes are uncommon. Instead, this potentially fatal arrhythmia is more frequently linked to other electrolyte problems, such as hypomagnesemia, or other causes, including QT-prolonging medicines [1].Though there are pathophysiological reasons for this, few studies have found a link between hypocalcemia and a higher risk of bad outcomes due to AKI. In unadjusted analysis, total blood calcium levels at the time of admission to the intensive care unit (ICU) in 210 critically sick people were found to be linked with a higher incidence of "renal failure" compared to levels of 8.5 mg/dL or greater (multivariable analyses were not conducted). Afshinnia et al. assessed iCa levels at initiation of renal replacement therapy (RRT) in 685 critically ill patients with severe AKI, and found no association [11]. Nevertheless, levels of iCa less than 1 compared to 1.15 mmol/L or higher were independently linked to an increased 60-day mortality when iCa was evaluated as a time-varying exposure. Lastly, research by Leaf et al. in a variety of contexts, including established AKI and critical illness, revealed no correlation between total serum calcium levels and outcomes linked to AKI [12].

1.5 Hypercalcemia and AKI

Following acute renal impairment brought on by ischemia and toxic shocks, the concentration and content of calcium in tubular cells increases. Given that the proximal tubule is thought to be a significant site of injury in acute renal failure and that calcium is essential for numerous cell functions, it is plausible that cell calcium overload directly contributes to the pathophysiology of acute renal failure. Increased calcium levels in tubular cells have been linked to changes in the function of the cytoskeleton, mitochondria, endoplasmic reticulum, and plasma membrane. Even though there is evidence that calcium plays a part in acute renal injury, more research is necessary to fully understand the significance of cell calcium overload. Additionally, some elements of acute renal failure and recovery may be related to changes in extracellular calcium and mineral metabolism. Acute renal failure may benefit from the use of calcium channel blockers and other therapies that control variations in calcium levels [13]. Sometimes patients have hypercalcemia and AKI when they first arrive. The coexistence of hypercalcemia with AKI may be crucial for two reasons: first, hypercalcemia may play a major role in the development of

the AKI, and second, it may serve as a warning sign for the clinician to rule out other possible causes of the AKI [14]. Many mechanisms exist through which hypercalcemia can directly cause AKI, including afferent arteriolar vasoconstriction, which results in a decreased glomerular filtration rate; calcium binding to the CaSR on the thick ascending limb's basolateral membrane, which causes the sodium-potassium-chloride cotransporter to be down-regulated and causes natriuresis and volume depletion; and nephrogenic diabetes insipidus, which is brought on by increased autophagic degradation of aquaporin-2 channels in the inner medullary collecting ducts. Furthermore, nephrolithiasis, nephrocalcinosis, and hypercalciuria can result from hypercalcemia and induce both acute and long-term renal damage [15].

1.6 Mechanisms of hypercalcemia in AKI

Excessive intestine absorption, renal retention of calcium, excessive bone resorption, or a combination of these disorders can all lead to hypercalcemia. Patients with acute renal failure (ARF) often exhibit hypocalcemia, with a reduction in both the total plasma calcium and ionised calcium fractions [16] as shown in figure (1). Hypercalcemia could be an indication of further morbidities. In addition, hypercalcemia may exacerbate renal vascular contraction, cause hypertension, and worsen tubular necrosis, which is commonly observed in ARF cases. Multiple myeloma is often associated with hypercalcemia. There seems to be a higher risk of renal injury in people with IgD and light chain myeloma. In 43% of the instances in research including 56 patients with myeloma and severe renal failure, hypercalcemia or nonsteroidal anti-inflammatory drugs were found to be possible precipitants of renal failure. The main factors influencing survival in myeloma patients are their reaction to chemotherapy and their ability to enter a stable plateau phase. Renal function improved in these two patients when serum calcium levels dropped. Before his serum creatinine levels could return to normal, one patient passed away [17].

1.7 Management of hypercalcemia in cases of AKI

In order to help lower serum calcium levels and restore the relative water and volume deficits, it is recommended to hydrate with isotonic saline. Utilizing the connection between sodium transport in the proximal tubule and ascending limb of Henle, the 0.9% saline solution [18]. When treating hypercalcemia, furosemide and sodium chloride infusions are commonly utilised. The aim is to impede the ascending limb of Henle's ability to reabsorb calcium, hence elevating calciuresis [19]. Forced saline diuresis, however, might not be safe or effective enough, especially for individuals who have severe renal failure. When severe renal failure makes it impossible to give hypercalcemic patients substantial amounts of intravenous fluids, calcium-free hemodialysis is appropriate in these situations. As long as the predialysis plasma calcium level is high, a single 2- to 3-hour treatment with a calcium-free dialysate is safe [18]. The majority of the time, high levels of calcitonin and bone resorption cause hypercalcemia; biphosphonate or mithramycin are typically also needed. One crucial treatment strategy for acute hypercalcemia is calcitonin. Similar to bisphosphonates, calcitonin promotes calcium excretion through the urine while simultaneously blocking osteoclast bone resorption. The main benefit of calcitonin is how quickly it works; it can reduce serum calcium levels to their maximum in 12 to 24 hours. The primary drawback of calcitonin is its lack of potency [19]. Serum calcium levels appear to drop quickly when calcitonin and etidronate or pamidronate are used in combination therapy. The prolonged decrease over multiple days is definitely caused by the bisphosphonate [17, 19]. One of the first-choice medications for the treatment of hypercalcemia was once mithramycin. Similar to other anticalcemic medications, the decrease in serum calcium levels is typically not long-lasting. Because mithramycin has the potential to produce a number of unfavourable side effects, including hepatotoxicity and nephrotoxicity, it has been replaced as a first-line medication by the bisphosphonates, either with or without calcitonin. This medication is currently kept on hand for extremely challenging and uncommon circumstances [18, 19].

1.8Albumin level and AKI

Albumin also is an important protein synthesized by the liver with multiple vital functions including osmotic pressure regulation, a carrier of poorly water-soluble molecules, antioxidant and anti-inflammatory effects [20]. In addition to the albumin role in maintenance of plasma volume by preserving colloid osmotic pressure, it also provides many physiological effects, including coupling and carrying various endogenous and exogenous toxic substances, scavenging free radicals, maintaining capillary membrane permeability, providing a physiological reservoir of nitric oxide, imparting an anti-inflammatory effect and inhibition of apoptosis. Several studies have suggested that serum albumin can preserve the kidneys from toxic agents and maintain optimal oncotic pressure and kidney perfusion [21]. Elevated serum albumin levels have been described in patients with dehydration and high protein diet consumption. Although high protein diets can increase albumin synthesis, albumin only increases by small increments and high serum albumin levels ≥4.5mg/dL are mostly caused by volume depletion [22]. Hypoalbuminemia is prevalent among hospitalized patients, with an incidence ranging from 16% up to 82%. Studies have shown associations of hypoalbuminemia with AKI and mortality in various clinical settings including general hospitalized patients especially intensive care unit (ICU). Conversely, there are no studies that reported data on the incidence and effects of elevated serum albumin among patients admitted to the hospital [20]. Several factors can influence hypoalbuminemia including inflammation and/or infections, malnutrition and/or protein-losing disorders, oxidative stress, cancer cachexia, and liver dysfunction. Thus, hypoalbuminemia may indicate the severity of an underlying disease and/or a marker of malnutrition. In addition, studies have also consistently demonstrated that hypoalbuminemia is independently associated with increased risks of AKI development and mortality in critically ill patients [21]. Thus, intravascular volume depletion likely explains the association between elevated admission serum albumin and an increased risk of AKI. This likely explains why the AKI severity in the setting of elevated serum albumin ≥4.5mg/dL is lower, compared with AKI occurring in patients with serum albumin levels ≤2.4mg/dL who may have more severe underlying illness. On the contrary, death was lowest for those with serum albumin

levels ≥4mg/dL. Additionally, these findings support our assumption that increased rates of lower stages of AKI among patients with serum albumin levels ≥4.5 mg/dL are mostly due to volume depletion [23].

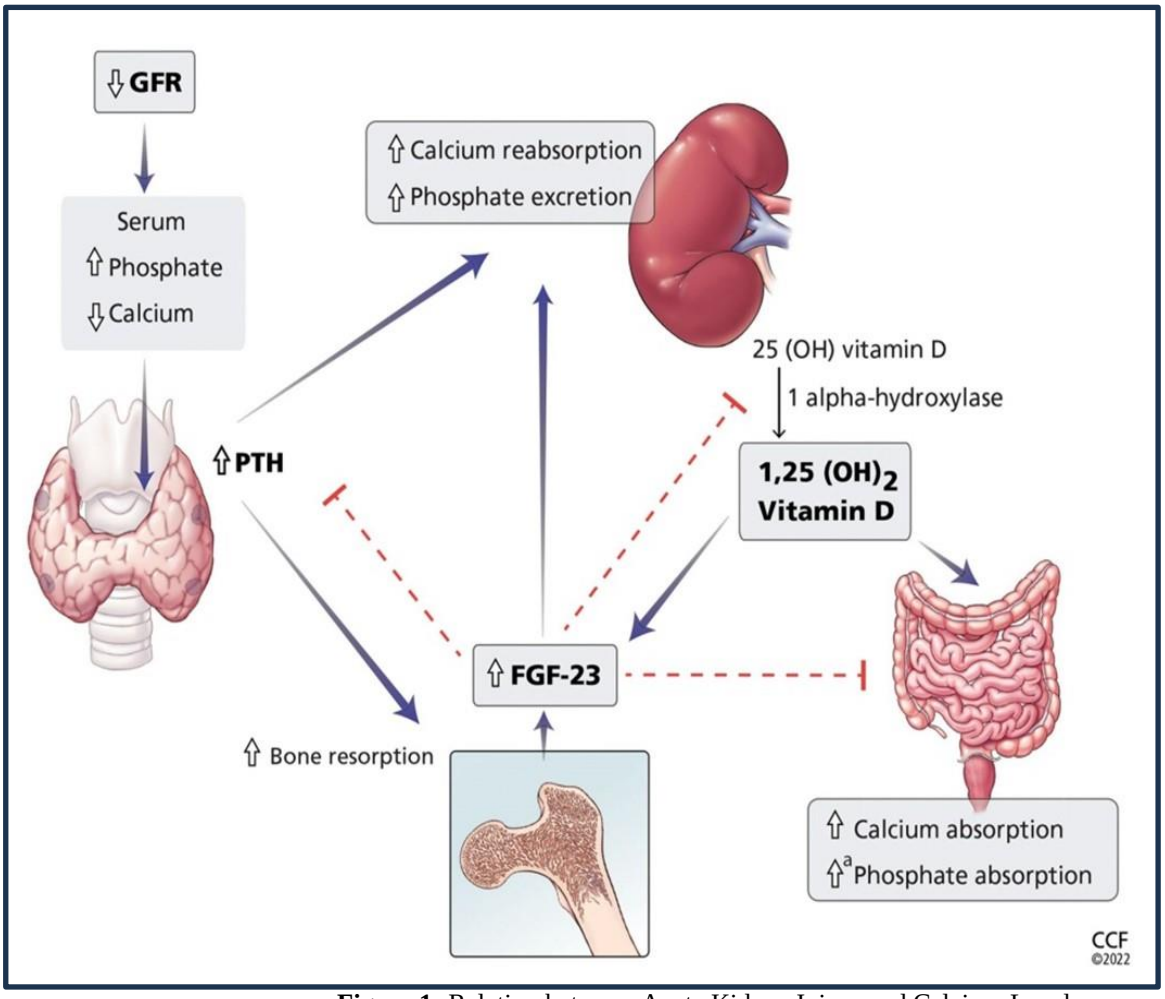

Figure 1: Relation between Acute Kidney Injury and Calcium Level

1.9 Measurement of circulating calcium levels in AKI

Two methods are available in routine clinical practice for the assessment of circulating calcium levels: total serum calcium and plasma ionized calcium (iCa). iCa is considered the gold standard assessment of physiologically relevant free calcium levels in the circulation because total serum calcium measurements assess both biologically active (45%) and biologically inactive (55%) calcium. The latter is bound to albumin and other organic and inorganic anions such as sulfate, phosphate, and citrate [24]. Clinicians frequently rely on total serum calcium levels because measurement of iCa is more cumbersome: the samples must be drawn in a heparinized syringe, transported on ice, and processed immediately. A comparative study of total serum calcium, albumin-corrected total serum calcium, and iCa levels in patients with AKI has not been performed. However, it is likely that assessment of total serum calcium levels with or without correction for hypo-albuminemia will often fail to accurately identify hypocalcemia, normocalcemia, or hypercalcemia in patients with AKI because multiple factors other than the serum albumin concentration affect the proportion of total serum calcium that is ionized [15]. These factors, which frequently are present in patients with AKI, include acid-base disorders, hyperphosphatemia, hyperparathyroidism, and transfusion of blood products with citrate-containing preservative solutions. Furthermore, albumin-corrected total serum calcium equations (which is corrected calcium = serum calcium + 0.8 * (4 - serum albumin)) have been shown to be unreliable in other clinical settings, such as critical illness, CKD, end-stage renal disease, and among patients suspected of having calcium metabolic disease [25].

2. Conclusion and recommendations

We concluded that hypocalcemia is a common condition in AKI. Total and adjusted calcium levels at baseline are linked to hypocalcemia in AKI. For the purpose of early correction and complication avoidance, serum corrected calcium levels in all AKI patients must be measured. In order to improve outcomes for AKI patients in the ICU, serum calcium measurements in these patients must be performed every 4-6 hours and maintained at 8–9 mg/dl. To validate our findings, multicenter collaboration is required for more clinical investigations.

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Conflicts of interest

The authors affirm that they have no conflicts of interest.

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