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Role of calcium, magnesium, and zinc in the management of hypocalcemia: A review

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Abstract
A prevalent electrolyte imbalance in hospitalized and severely ill patients, hypocalcemia is linked to serious cardiovascular and neuromuscular problems. Reduced parathyroid hormone activity, vitamin D inadequacy, renal failure, and imbalances in minerals are all part of its pathophysiology. While zinc supports bone metabolism, immunological response, and cellular regulation, magnesium deficiency decreases parathyroid hormone release and action, highlighting their interdependent roles in calcium homeostasis. Mild paresthesia to potentially fatal tetany, convulsions, and cardiac arrhythmias are examples of clinical symptoms. Acute intravenous calcium therapy, long-term oral calcium and vitamin D supplementation, and correction of related mineral deficiencies are all part of management, which varies according to severity and origin. The pathogenesis, prevalence, clinical characteristics, and treatment of hypocalcemia are discussed in this review, with a focus on the therapeutic value of supplementing with calcium, magnesium, and zinc.

Keywords: *Pterospermum acerifolium*, Muchkunda, Ayurveda, Kanak Champa, medicinal plant, pharmacological activities, phytochemistry

Introduction
Compared to hypercalcaemia, hypocalcaemia is more prevalent in hospital patients and is linked to serious neuromuscular and cardiovascular problems. Parathyroid hormone (PTH) levels can be low, normal, or dysfunctional, depending on the underlying cause. Conditions including acute pancreatitis, starved bone syndrome, and magnesium shortage, which frequently occur with normal or decreased serum phosphate levels, are typically the cause of hypocalcaemia. Patients with severe primary hyperparathyroidism typically experience hungry bone syndrome following parathyroidectomy, which is the primary cause of long-term postoperative hypocalcaemia [1].
Hypocalcaemia is defined clinically as a blood calcium concentration of less than 8.5 mg/L or a serum calcium ionized level of less than 1.0 mmol/L. The symptoms include tetany, laryngospasm, muscle spasms, and mild peripheral numbness and paresthesia. Congestive cardiac failure, convulsions, and syncope are examples of serious situations. Neuromuscular hyper excitability, QT prolongation, Trousseau-like symptoms, or Chvostek-like symptoms may be discovered during a physical examination [2].
In individuals with inflammatory bowel illnesses, adequate vitamin D levels are crucial for immunomodulatory effects as well as bone mineralization [3].

Pathophysiology of hypocalcemia
Disruptions in calcium intake, excretion, and hormone regulation lead to hypocalcemia. Magnesium, vitamin D, and parathyroid hormone are the main regulators of calcium homeostasis. If magnesium levels are not sufficiently recovered, a magnesium deficit can prevent parathyroid hormone (PTH) from being secreted and cause resistance to its effect, rendering hypocalcemia resistant to calcium therapy. Moreover, phosphate balance and renal tubular processing are closely linked to calcium metabolism, highlighting the delicate control of serum calcium levels [4].

Calcium
The mineral calcium is involved in several essential processes [5]. One essential component that is vital to the mineralization of the skeleton is calcium.

Hydroxyapatite, which makes up more than 99% of the body's calcium, is kept in bone and serves as a reservoir for calcium that may be released into the serum in addition to strengthening the skeleton [6]. Osteopenia and osteoporosis are caused by a prolonged lack of calcium consumption. Supplementing with calcium is often used to prevent and cure osteoporosis [7]. Calcium requirements vary throughout life, increasing during periods of growth, pregnancy, and lactation [8]. In order to promote bone regeneration, the release of calcium and phosphorus ions controls the activation of osteoblasts and osteoclasts [9]. Bone resorption and secondary hyperparathyroidism are caused by insufficient calcium intake. In addition to its skeletal function, calcium controls muscle contraction, mast cell degranulation, and insulin secretion. Because calcium-dependent cell adhesion molecules malfunction, disruptions in calcium homeostasis have been linked to inflammatory conditions like psoriasis [10, 11].

Magnesium

In the human body, magnesium (Mg^{2+}) serves a variety of purposes. It is a cofactor for over 300 enzymes and controls various basic processes, including blood pressure, muscle contraction, neuromuscular conduction, glycemic regulation, and cardiac contraction [12]. The ability of human cells and systems to function depends on magnesium (Mg^{2+}). However, this mineral is frequently disregarded in favor of other cations like iron or calcium. About 25 grams of magnesium, the fourth most prevalent element in the human body, are mostly found in bones [13]. Nearly 60% of the body's magnesium is stored in bone, making it an essential mineral for bone metabolism. It acts as a reservoir to keep plasma magnesium levels stable and affects osteoblast and osteoclast activity. Increased bone mineral density and a lower risk of fracture are linked to adequate magnesium consumption. Additionally, magnesium has a biphasic effect on bone regeneration, highlighting the significance of taking supplements in a balanced manner [14]. The effects of magnesium on cardiovascular health are among its most prominent health advantages. By encouraging vasodilation and minimizing arterial stiffness, it lowers the risk of heart disease, helps control blood pressure, and improves bone health by assisting in calcium (Ca) absorption and bone mineralization, which is crucial for preventing osteoporosis. Additionally [15].

Zinc

Both innate and adaptive immune cells are impacted by zinc, which is crucial for the immune system. Zinc deficiency has been linked to a weakened immune system and an increased vulnerability to infection, according to numerous research [16]. Zinc has a positive influence on growth and development. One of the main reasons for this positive effect is the involvement of zinc in the bone metabolism [17]. Development and growth are positively impacted by zinc. Zinc's role in bone metabolism is one of the primary causes of this beneficial effect. Zinc is mostly absorbed in the small intestine, where it is more efficiently absorbed from liquids (up to around 70%) than from solid foods (about 30%) [18]. Heart conditions like hypertension and atherosclerosis have been connected to zinc deficiency [19]. Growth retardation, immunological dysfunction, diarrhea, baldness, and cognitive impairment are just a few of the consequences associated with zinc deficiency. Zinc levels in bone are lowered by aging, bone resorption, and postmenopause [20].

Interaction of calcium magnesium and zinc

Trace elements like iron (Fe), zinc (Zn), copper (Cu), calcium (Ca), phosphorus (P), and magnesium (Mg) also influence bone formation and metabolism. Both excess and deficiency of the trace elements are thought to be risk factors for the emergence of bone disorders including osteoporosis [21]. Type-1 nutrient deficiencies (iron, calcium, iodine, vitamins A and B) show up as store reductions followed by functional plasma components, while type-2 nutrient deficiencies (zinc, protein, sodium, and water) cause clinical symptoms like stunted growth before functional plasma levels decline [22]. Maintaining the physiologic activities of different organs requires a proper balance of magnesium and vitamin D. In order to maintain good bone functioning, vitamin D helps control the balance of calcium and phosphate [23]. More than 95% of patients with osteoporosis had at least one concomitant condition, according to a new cross-sectional investigation conducted in Germany with over 10,000 participants who were 50 years of age or older. As a population ages, multimorbidity becomes more common, which eventually results in polypharmacotherapy. In the elderly, polypharmacotherapy is a serious concern. Forty percent of people in institutions take more than nine medications every day [24]. Numerous studies have been conducted since zinc's significance for human health was originally identified. Many metabolic and chronic diseases, such as diabetes, cancer (such as esophageal, hepatocellular, breast, and colon cancer), neurodegenerative diseases like Alzheimer's disease, and intestinal disorders like inflammatory bowel disease and irritable bowel syndrome, are now known to be significantly impacted by zinc, particularly zinc deficiency [25]. Since zinc's importance for human health was first recognized, numerous research have been carried out. Zinc, especially zinc deficiency, has been shown to have a major impact on a number of metabolic and chronic diseases, including diabetes, cancer (including esophageal, hepatocellular, breast, and colon cancer), neurodegenerative diseases like Alzheimer's disease, and intestinal disorders like inflammatory bowel disease and irritable bowel syndrome [26].

Role of combination therapy (Calcium + Magnesium + Zinc)

Calcium supplementation should not be the only method used to treat hypocalcemia. While zinc promotes the production of bone matrix, magnesium supplements enhance calcium absorption and restore PTH responsiveness. Research indicates that as compared to calcium monotherapy, mixed mineral supplementation offers better benefits in bone mineral density and metabolic outcomes, especially in older people and patients with chronic illnesses.

[27, 28]. Magnesium and zinc both play significant roles in lipoprotein metabolism and glucose regulation. Magnesium is a cofactor in several adenosine triphosphate-dependent processes that are crucial for insulin action and the metabolism of carbohydrates [29]. Magnesium (Mg) is the fourth most abundant element in the human body ($Ca^{2+} > K^{+} > Na^{+} > Mg^{2+}$) and the second most abundant cation within the body's cells after potassium. Mg^{2+} contributes to the skeleton's structural makeup along with calcium and phosphorus [30].

Clinical management of hypocalcemia

Serum levels of phosphate, magnesium, albumin, and bicarbonate all have an impact on serum calcium levels. The measurement of the total calcium level is altered by the

change in albumin concentration, but the blood level of ionized calcium remains unchanged [31]. The severity of the calcium deficit, the speed at which it manifests, the existence of symptoms, the likelihood of potentially fatal consequences, and the underlying cause all influence how hypocalcemia is treated. In order to prevent recurrence, the therapeutic objective is to return serum calcium concentrations to normal while also treating the underlying cause [32]. Conventional therapies for patients with symptoms include oral supplements of calcium and/or activated vitamin D, which is the 1-alpha hydroxylated form of 25-OH vitamin D3, usually calcitriol or alfacalcidol. In the absence of normal parathyroid function, supplementation can cause or worsen pre-existing hypercalciuria, raising the risk of long-term renal problems like nephrocalcinosis, nephrolithiasis, and impaired renal function, even though conventional therapy can raise blood levels of Ca2+ [33].

Prevalence of hypocalcemia

Although the clinical features of individuals infected with 2019-nCoV have been described in a number of investigations, hypocalcemia in COVID-19 patients has not yet been documented. The frequency of hypocalcemia in critically ill patients varies from 15% to 88% in adults [34]. The range of the definition was < 0.9 mmol to < 1.16 mmol/L. 56% (95%) of patients had hypocalcemia when they arrived at the emergency department. CI 37%-74%, [35]. In the initial clinical trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months, FREEDOM trial), the prevalence of hypocalcemia following denosumab injection was less than 1% [4, 6], while reports on real-world data show a higher prevalence of 4-26% [36]. According to our laboratory's reference range, a serum calcium value of 8-11 mg/dl was deemed normal, a value of less than 8 mg/dl was deemed hypocalcemia, and a value of more than 11 mg/dl was deemed hypercalcemia [37]. 97% (N=152) of trauma patients who received huge transfusions after a 1:1 PRBC to plasma ratio were found to have hypocalcemia in a single-center retrospective assessment; 71% of these patients had severe hypocalcemia ionized calcium [38].

Incidance of Hypocalcemia

According to reports, the prevalence of hypocalcemia can reach up to 85% in intensive care units and 18% in hospitalized patients [39]. Three categories of hypocalcemia were identified: Mild (total serum calcium 8.0-8.39 mg/dL), moderate (7.5-7.99 mg/dL), and severe (less than 7.5 mg/dL) [40]. In clinical practice, one of the most frequent postoperative consequences after thyroid surgery is transient hypocalcemia. According to reports, there is a ≤ 2% incidence of chronic malfunction, while the rate of postoperative transitory hypocalcemia ranges from 6% to 30% [41]. Compared to 2.95% of patients without hypocalcemia, 12.4% of PE (acute pulmonary embolism) patients with hypocalcemia passed away in the hospital [42].

Limitations and Future Perspectives

Randomized clinical trials assessing the combined use of calcium, magnesium, and zinc in the treatment of hypocalcemia are still scarce, despite evidence supporting their individual functions. Future research should concentrate on long-term safety, clinical efficacy in a range of patient demographics, and ideal dosage ratios [43]. Higher calcium dosages may be necessary while the patient and provider wait for the parathyroid gland to heal, which can take weeks. Pre- and post-operative PTH levels have been suggested by someresearch as a way to assess the necessity of calcium supplementation [44]. This prospective multicenter trial recruited 400 patients between January 2015 and April 2017. Due to a variety of thyroid conditions, every patient had a complete thyroidectomy [45]. The areas under the curve (AUC) that were validated both internally and externally were 0.860 and 0.862, respectively [46]. Future prospective studies should assess the potential clinical benefit of preventive therapy for hypocalcemia in high-risk patients using indicators similar to those we and others propose [47].

Treatment

Acute Treatment

Quick serum calcium correction is essential for patients with severe or symptomatic hypocalcemia. To quickly reduce neuromuscular irritability, tetany, seizures, and possible cardiac arrhythmias, intravenous calcium, most frequently calcium gluconate, should be given with cardiac monitoring. Depending on the clinical response and serum calcium levels, a continuous infusion may come after the initial bolus therapy [48].

Chronic Management

The cornerstone of treatment for persistent or asymptomatic hypocalcemia is oral calcium supplementation (often calcium carbonate in divided dosages) in conjunction with vitamin D or its active metabolites, such as calcitriol, to maintain calcium homeostasis. To maximize treatment and minimize problems, related hypomagnesemia must be corrected, and blood calcium and phosphorus levels must be regularly monitored [49].

Emerging and Adjunctive Therapies

Recombinant human parathyroid hormone (rhPTH 1-84) replacement has demonstrated effectiveness in stabilizing serum calcium and lowering the need for conventional supplementation in certain patients, particularly those with chronic hypoparathyroidism. This offers a novel therapeutic option where traditional approaches are insufficient [50].

Conclusion

Due to intricate disruptions in hormone regulation and mineral metabolism, hypocalcemia is still a common and clinically significant illness. Although calcium supplementation is necessary, concurrent magnesium and zinc deficits must be corrected for successful and long-term therapy. These minerals work in concert to preserve calcium balance, bone health, and metabolic stability. When compared to calcium alone, combination therapy may provide better results, especially in chronic and high-risk disorders. To determine the best dosage plans and long-term safety, more clinical research is necessary to establish an integrated approach to managing hypocalcemia

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