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Review Article

Dependent and independent causes of hypercalcemia

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ABSTRACT

Previous clinical studies show that the condition is significantly associated with mortality and increased cardiovascular morbidities. Accordingly, it is essential to conduct adequate diagnosis and evaluation to assess these cases properly. Studies show that different etiologies have been associated with hypercalcemia development with variable prevalence rates among different populations. Reduced PTH levels among patients with hypercalcemia indicate the presence of a non-PTH-dependant etiology for hypercalcemia. We have discussed various causes of hypercalcemia, including dependant and non-dependant causes. We found that malignancy-induced hypercalcemia is the commonest non-PTH-dependant etiology of hypercalcemia. Many malignancies were reported in the literature to attribute to the development of hypercalcemia. Vitamin D-mediated hypercalcemia was also reported as another common etiology for the condition. It might occur secondary to overdosing, immobilization, endocrine disorders, and granulomatous diseases. Other familial and congenital causes were also reported in the literature and discussed.

Keywords: Hypercalcemia, Etiology, Parathyroid, Parathormone, Vitamin D, Calcium

INTRODUCTION

Calcium metabolism is regulated by the actions of vitamin D (1,25(OH)$_2$Vit D) and parathormone (PTH) on the bone, gut, and kidneys (Figure 1). Due to different factors and etiologies, high calcium levels (hypercalcemia) have been reported to be common among the different age groups. Moreover, previous clinical studies show that the condition is significantly associated with mortality and increased cardiovascular morbidities. Therefore, it is critical to identify patients with hypercalcemia to adequately treat them and apply better interventions to decrease the burden of the disease.[1]

Before establishing the diagnosis, it is essential to identify the underlying etiology. Studies show that different etiologies have been associated with hypercalcemia development with variable prevalence rates among

different populations.[2] However, it has been shown that primary hyperparathyroidism is the commonest cause among various population groups. On the other hand, malignancy was the commonest cause among other settings, and primary hyperparathyroidism is the second commonest cause. This indicates wide variations in the incidence of causes of hypercalcemia, which clinicians should consider when evaluating these patients.[3] The present study aims to elaborate on the different dependant and non-dependant causes of hypercalcemia based on evidence from relevant studies.

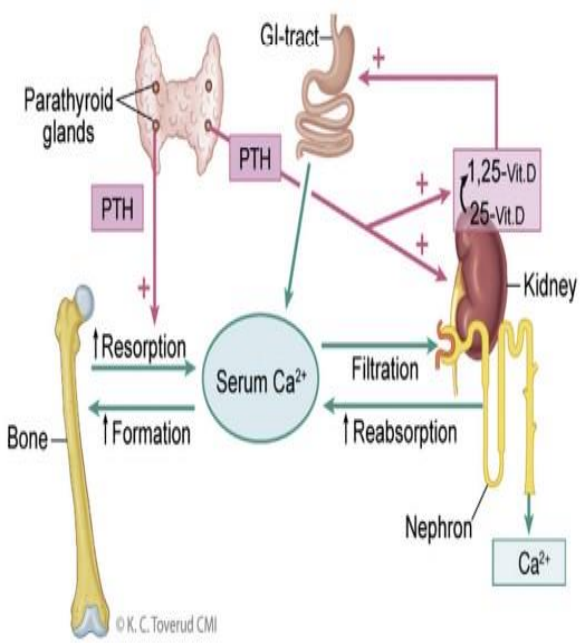

Figure 1: Parathormone-mediated calcium homeostasis.[1]

LITERATURE REVIEW

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 27th November 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google Scholar while the reference lists of the initially included papers. Papers discussing dependent and independent causes of hypercalcemia were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

DISCUSSION

PTH-dependant hypercalcemia

Hypercalcemia that occurs secondary to PTH-dependent causes is most commonly attributed to parathyroid tumors, leading to primary or tertiary hyperparathyroidism development. Thus, primary hyperparathyroidism might occur as a single disorder and be part of another syndrome. On the other hand, evidence shows that chronic renal failure is usually associated with tertiary hyperparathyroidism. Therefore, adequate evaluation should be conducted before establishing the diagnosis of the presenting children to enhance the line of treatment and related outcomes. In addition, gestational maternal hypocalcemia was previously associated with PTH-dependant hypercalcemia in children, but as non–parathyroid tumor-related etiology.[4]

It has been indicated that hyperparathyroidism occurs in all types of multiple endocrine neoplasias (MEN). In this context, it has been shown that most patients presenting with these conditions usually suffer from hypercalcemia as their first presentation.[5-7] It has been furtherly shown that hypercalcemia might also be associated with patients suffering from hyperparathyroid jaw-tumor syndrome.[7] These syndromes are attributed to different genetic mutations. Therefore, it has been recommended that biochemical surveillance to detect abnormal parathyroid levels is essential to intervene against the development of these disorders. In addition, PTH-dependant hypercalcemia might also occur as a non-syndromic event. For instance, studies indicate that familial hypocalciuric hypercalcemia is a direct cause for developing hypercalcemia. However, these studies suggested that hypercalcemia is more probably attributed to impaired renal functions and not due to parathormone levels.[8] Familial isolated hyperparathyroidism was also reported in the literature as a potential cause for hypercalcemia related to PTH levels. It has been shown that patients suffering from this condition usually develop primary hyperparathyroidism irrespective of other tumors that might alter PTH levels. It has been shown that the development of hypercalcemia in these patients usually occurs within ten years after the pathology of the condition has been documented.[9] Evidence shows that neonatal severe primary hyperparathyroidism might also cause similar events in the same context. Evidence indicates that the condition might be lethal if left untreated within three months. Many pathological events were reported in the affected patients, including bone demineralization, respiratory distress, hypotonia, and hypercalcemia.[10,11]

In addition to the PTH-dependant causes, various investigations in the literature have assessed the impact of different causes that can affect calcium levels leading to hypercalcemia, which will be discussed in the current section.

Vitamin-D-related causes

Accidental overdosing and incorrect prescriptions of vitamin D can significantly lead to hypercalcemia secondary to vitamin D intoxication.[12-15] It has been further demonstrated that high doses of vitamin D might also be complicated with hypercalcemia when used in

therapeutic doses to treat patients with cystic fibrosis and rickets.[16-19] Unfortunately, the mechanism and pathophysiology of the correlation between vitamin D levels and hypercalcemia has not been properly reported among the relevant studies. However, it has been previously shown that hypercalcemia is most probably not attributed to the actions of $1,25(OH)_2D_3$. In this context, many studies have assessed the association between hypercalcemia and increased serum levels of $1,25(OH)_2D_3$ in the affected patients. Furthermore, it has been demonstrated that increased levels of $1,25(OH)_2D_3$ might occur secondary to different conditions, including reduced renal excretion and catabolism of the active compound ($1,24,25(OH)_2D_3$), phosphate depletion-induced increased synthesis of $1,25(OH)_2D_3$ and overproduction of $1,25(OH)_2D_3$ secondary to excess activation of the 1α-hydroxylase enzyme.[2,20-22]

It has been demonstrated that children suffering from idiopathic infantile hypercalcemia usually suffer from nephrocalcinosis, hypercalciuria, and hypercalcemia secondary to excessive production of $1,25(OH)_2D_3$ concerning phosphate depletion and impaired activities of the 1α-hydroxylase enzyme. In this context, evidence shows that the condition is not usually permanent as most cases resolve by one year. However, the condition lasted into adulthood.[2] In addition, many granulomas and malignant diseases were also associated with increased synthesis and production of $1,25(OH)_2D_3$-induced hypercalcemia regardless of renal actions. Previous relevant studies showed that hypercalcemia and increased 1α-hydroxylase activities had been associated with increased production of $1,25(OH)_2D_3$ in association with different conditions, including Hodgkin's, non-Hodgkin's lymphomas, and ovarian dysgerminomas.[23,24] Hypercalcemia might also result from dysregulated production of $1,25(OH)_2D_3$ in many granulomatous conditions, including human immunodeficiency virus (HIV) immune reconstitution syndrome, tuberculosis, sarcoidosis, subcutaneous fat necrosis of the newborn, histoplasmosis, cytomegalovirus infection, Crohn's disease, cat scratch fever, fungal granuloma including coccidioidomycosis, and leprosy. In addition, evidence shows that hypercalcemia among patients suffering from subcutaneous fat necrosis of the newborn can be life-threatening.[1,3,4]

Malignancy

In addition to vitamin D-related hypercalcemia, it has been shown that many other conditions can lead to hypercalcemia, irrespective of vitamin D levels. For example, various previous studies demonstrated that hypercalcemia might be associated with many malignancies and related disorders, including dysgerminomas, hepatic tumors (including hepatocellular carcinoma and hepatoblastoma), neurological tumors (including neuroblastoma), rhabdomyosarcoma, and hematological malignancies (including myeloma, lymphomas, and leukemias).[3,25-28] However, it has been estimated that the incidence of these conditions in children might be less than 1%.[29] These patients' increased calcium levels might occur secondary to osteoclastic bone resorption and osteolysis secondary to leukemias and metastasis. The evidence further shows that hormones (including parathyroid hormone-related protein, or PTHrP) are responsible for developing these events in the affected patients. Various studies demonstrated some tumors (including renal dysplasia, multicystic dysplastic kidney disease, renal cell carcinomas, benign congenital mesoblastic nephroma, pheochromocytoma, ovarian and breast carcinomas, dysgerminomas, and squamous cell carcinomas) are associated with the systemic release of PTHrP. This has been cumulatively associated with hypercalcemia in the affected patients.[3,4,30-33]

Immobilization

Hypercalcemia might develop secondary to prolonged immobilization following serious injuries. For instance, it has been estimated that 10-23% of children suffering from spinal cord injuries developed hypercalcemia. This has been preceded by hypercalciuria and is due to the suppression of the parathormone hormone. Another study also reported that single-limb fractures were also associated with the development of immobilization hypercalcemia.[34] Maynard et al concluded that adolescents and males tend to have an increased risk of developing immobilization hypercalcemia, most probably due to the high bone mass and rapid growth.[35] However, it should be noted that this pathology is poorly understood and needs further elaboration, and is most probably attributed to bone metabolism and associated activities.

Renal tubular disorders

Evidence shows that hypercalcemia has been reported among patients with distal renal tubular acidosis.[36] Among other manifestations, hypercalcemia was also reported among patients with Bartter syndrome type 1.[37,38] However, it has been shown that the incidental hypercalcemia in these patients is attributed to a malignant increase in circulating parathormone levels.[39]

Vitamin A and drugs toxicities

The development of milk-alkali syndrome is secondary to the administration of inappropriate sodium and calcium bicarbonates in patients with impaired renal functions, prolonged administration of toxic doses of vitamin A and its derivatives, and thiazides have been associated with hypercalcemia. In addition, influencing the activities of osteoclastic-related bone resorption has been associated with administering Isotretinoin (13-cis-retinoic acid). However, it should be noted that the toxicity of vitamin A is a rare manifestation that is not commonly reported. It has also shown that hypercalcemia secondary to administration of thiazides usually results from increased reabsorption of calcium at the renal tubules.[4,40-42]

Endocrine disorders

Studies also reported that hypercalcemia could significantly develop secondary to various endocrine disorders, including severe congenital hypothyroidism, thyrotoxicosis, Addison's disease, and pheochromocytoma. Thus, PHTrP might be the leading cause of hypercalcemia in patients with pheochromocytoma.[31,33,43] On the other hand, increased intestinal calcium absorption might be the etiology of hypercalcemia in patients with Addison's disease.[44] This has been furtherly reported to be associated with an impairment in the levels of mineralocorticoid hormone. On the other hand, there is a significant impairment in the metabolism of many materials, including bone metabolism, among patients with thyrotoxicosis, resulting in hypercalcemia secondary to bone resorption.[45] In addition, many of them reported hypercalcemia in children with severe congenital hypothyroidism. However, the mechanism is not adequately comprehended, and the condition is usually asymptomatic in many affected children. In the same context, it has been shown that hypercalcemia might result from the administration of levothyroxine in these children, secondary to increasing $1,25(OH)_2D_3$ levels.[46,47]

Congenital diseases and inborn errors of metabolism

Hypercalcemia was also reported among children with different congenital diseases. For instance, it was reported that despite the normal levels of PTH, hypercalcemia and hypercalciuria were significantly associated with children suffering from Jansen's metaphyseal chondrodysplasia. Patients with down syndrome were also reported to suffer from nephrocalcinosis and hypercalcemia. However, these disorders are not very common with the syndrome. The pathophysiology of hypercalcemia in these patients is not adequately understood. However, some evidence indicates that it might be secondary to the increased calcium absorption as affected patients do not respond to the oral administration of calcium supplementation. In another context, studies show that 5-50% of children with Williams syndrome usually have hypercalcemia. It might develop as an autosomal-dominant disorder or might be sporadic. It should be noted that the condition usually subsides within weeks after the manifestations start. However, the exact mechanism of these events is not adequately reported.[48-50]

Nutritional disorders might also lead to the development of hypercalcemia in children. For instance, it has been shown that phosphate depletion and enriched calcium formulas are associated with hypercalcemia in children. Therefore, amelioration of the calcium/phosphate content in the diets of newly born infants is essential to avoid the development of hypercalcemia and associated complications in this population group. Other inborn disorders might include blue diaper syndrome, disaccharide intolerance, congenital lactase deficiency, and hypophosphatasia. Evidence shows that the latter condition is usually associated with impaired bone mineralization and around 30% of children usually develop hypercalcemia. It has been furtherly shown that the condition might also manifest with immobilized adults. In addition, nephrocalcinosis and hypercalcemia were also reported among patients with congenital lactase deficiency secondary to severe diarrhea and weight loss. Furthermore, it has been shown that nephrocalcinosis usually persists even after initiating a lactose-free diet. However, it has been shown that hypercalcemia usually subsides within weeks. A similar mechanism and events were also reported for patients suffering from a sucrose-isomaltase deficiency. Therefore, urgent efforts are needed to identify these children and adequately treat them.[3,4]

CONCLUSION

Reduced PTH levels among patients with hypercalcemia indicate the presence of a non-PTH-dependant etiology for hypercalcemia. Accordingly, it is essential to conduct adequate diagnosis and evaluation to assess these cases properly. We have discussed various causes of hypercalcemia, including dependant and non-dependant causes. We found that malignancy-induced hypercalcemia is the commonest non-PTH-dependant etiology of hypercalcemia. Many malignancies were reported in the literature to attribute to the development of hypercalcemia. Vitamin D-mediated hypercalcemia was also reported as another common etiology for the condition. It might occur secondary to overdosing, immobilization, endocrine disorders, and granulomatous diseases. Other familial and congenital causes were also reported in the literature and discussed.

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