Immobilisation hypercalcaemia

Abstract

Hypercalcaemia is a common metabolic abnormality and its differential diagnosis is vast. Immobility is an uncommon cause of hypercalcaemia. Immobilisation hypercalcaemia is independent of parathyroid hormone and is associated with low levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. In addition, it is characterised by elevated levels of markers of bone resorption and low levels of bone-specific alkaline phosphatase, highlighting an imbalance of bone remodelling favouring osteoclastic bone resorption. Although immobilisation hypercalcaemia is a diagnosis of exclusion, physicians need to be aware of this condition to avoid excessive and invasive investigations when all other causes of parathyroid hormone-independent hypercalcaemia have been excluded. Management of immobilisation hypercalcaemia revolves around early mobilisation and rehabilitation together with pharmacotherapeutic agents such as intravenous isotonic saline, calcitonin and bisphosphonates. Denosumab may be a potential alternative yet off-label treatment for immobility hypercalcaemia in patients with renal insufficiency.

Key words: Bisphosphonates; Denosumab; Hypercalcaemia; Immobilisation; Rehabilitation

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Introduction

Hypercalcaemia is a common metabolic disorder with a broad differential diagnosis. Primary hyperparathyroidism and malignancy account for most cases of hypercalcaemia, but it has also been attributed to inherited conditions, endocrine-related conditions and certain medications (Vakiti and Mewawalla, 2021).

A lesser known cause of hypercalcaemia is immobility. Immobilisation-associated hypercalcaemia was first documented by Albright et al (1941). It occurs as a result of an imbalance of bone remodelling, where the rate of osteoclastic bone resorption exceeds the rate of osteoblastic bone formation. Increased bone resorption leads to hypercalciuria and eventually hypercalcaemia, once the renal capacity to excrete calcium is exceeded (Malberti, 2013).

This condition is typically seen in children and young adults, men in particular, as these tend to have a higher peak bone mass and higher rates of bone turnover, making them particularly prone to hypercalcaemia after prolonged immobilisation (Tettero et al, 2021). Patients with renal impairment are also at a higher risk of developing this condition (Uehara et al, 2017).

This review is based on the relevant guidelines and literature found via a Medline search from 1941 to 2022. The key words used were 'bisphosphonates', 'denosumab' and 'immobilisation hypercalcaemia'. Additional pertinent publications were manually obtained from other cited papers in retrieved articles. This review explores the pathophysiology of immobilisation hypercalcaemia and outlines its definition and management.

Pathophysiology

Prolonged immobilisation is associated with several molecular mechanisms that disrupt bone remodelling (Feng and McDonald, 2011).

One of these mechanisms involves the Wnt signalling pathway. Wnt signalling induces differentiation of osteoblast precursors into mature osteoblasts and prevents osteocyte and osteoblast apoptosis by inhibiting the β-catenin destruction complex (Guañabens et al, 2014).

This process is initiated by the Wnt-protein ligand binding to its dimeric cell surface receptors on osteoblasts, that is to the low-density lipoprotein receptor-related proteins (LRP) 5/6 and the seven transmembrane frizzled proteins. Wnt binding to the latter receptors leads to

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translocation of the cytoplasmic scaffolding protein dishevelled (Dvl). Wnt binding and Dvl recruitment by the frizzled receptor leads to LRP5/6 phosphorylation and activation. This results in the recruitment of axin to the membrane where it binds to Dvl (MacDonald et al, 2009).

Axin is a scaffolding protein that binds the various components making up the β-catenin destruction complex, which is responsible in targeting β-catenin for ubiquitination thus promoting its breakdown. Axin translocation results in the disassembly of this destruction complex, and hence to the stabilisation and accumulation of β-catenin (MacDonald et al, 2009). Therefore, Wnt actisvation allows the cytoplasmic protein ß-catenin to accumulate and translocate into the nucleus, where it subsequently activates the transcription of target genes responsible for the differentiation, proliferation and functionality of osteoblastic cells (Gaudio et al, 2010).

The Wnt signalling pathway can be antagonised by dickkopf-1 and sclerostin, both mainly produced by osteocytes. Dickkopf-1 internalises the LRP6 cell surface receptor through endocytosis, whereas sclerostin competitively binds to the LRP5 co-receptor (Gaudio et al, 2010). Therefore, these proteins interfere with the formation of the Wnt-LRP5/6-Frizzled receptor complex, blocking Wnt activity.

Studies have revealed that, in both mice and humans, immobilisation leads to excessive production of sclerostin, leading to reduced osteoblastic bone formation (Gaudio et al, 2010).

Immobilisation has also been associated with a high ratio of receptor activator of nuclear factor-κB ligand (RANKL):osteoprotegerin, which also contributes to enhanced bone resorption. RANKL is produced by osteoblastic stromal cells, and can also be produced by T cells as part of the inflammatory response. RANKL binding to the RANK receptor on osteoclast precursor cells acts as a potent inducer of osteoclast formation, stimulating bone resorption. On the other hand, osteoprotegerin, also produced by osteoblasts, helps protect bone from excessive resorption by binding to RANKL with high affinity, preventing it from binding and activating RANK (Boyce and Xing, 2008).

The net effect of these processes is the efflux of calcium from bone into the circulation. Hypercalcaemia occurs once the renal capacity to excrete calcium is exceeded. This explains why immobilised patients with renal impairment or those with pre-existing states of high bone turnover, such as adolescents, patients with Paget's disease, thyrotoxicosis or primary hyperparathyroidism, have a higher risk of developing hypercalcaemia (Malberti, 2013).

Other mechanisms that may contribute to hypercalcaemia in the immobilised patient have been reported. Nierman and Mechanick (2000) state that chronically critically ill patients (that is patients who survive an acute critical illness but remain debilitated and ventilator dependent) may be at a higher risk of immobility hypercalcaemia. They suggest that this may be the result of bone hyperresorption which is independent of parathyroid hormone and possibly the result of bi-directional interactions between the hypothalamic–pituitary–adrenal axis and the immune system. It has also been proposed that loss of sympathetic activation of bone in patients with spinal cord injury may also contribute to hypercalcaemia, as this may lead to reduced bone mineralisation and increased bone resorption (Tettero et al, 2021). However, further studies are required.

Symptoms and signs

The classical textbook presentation of 'stones, bones, groans and psychic moans' is less common nowadays, as hypercalcaemia is more frequently detected incidentally on routine biochemical investigations (Crowley and Gittoes, 2013).

The myriad of pain symptoms may be secondary to gastrointestinal upset as a result of constipation or peptic ulceration, musculoskeletal pain, or renal colic resulting from nephrolithiasis. Hypercalcaemia may exert psychological influences, with depression or cognitive decline being possible symptoms. It may have neurological presentations including weakness, asthenia, seizures and even coma (Sadiq et al, 2021). Association with nephrogenic diabetes insipidus results in polyuria and polydipsia. Hypercalcaemia may also have deleterious effects via arrhythmias such as torsade de pointes and ventricular fibrillation as a result of QT interval shortening (Turner, 2017).

There are no eponymous symptoms and signs for hypercalcaemia of immobility. Immobility itself is the major clue for this diagnosis. Risk factors for immobility should always be assessed.

These include increasing age, surgery, neurological conditions such as cerebrovascular accidents, spinal cord injuries and polyneuropathies, fractures and burns. Renal function should also be noted, as patients with acute renal insufficiency or pre-existing renal impairment have a higher risk of developing immobility hypercalcaemia (de Beus and Boer, 2012).

Therefore, it is very important to appreciate that new symptoms such as confusion, delirium, constipation, polyuria and polydipsia in the immobile patient may be caused by the development of hypercalcaemia, particularly in patients with any of the risk factors described above (Wick, 2007).

Investigations and diagnosis

Hypercalcaemia of immobilisation is a diagnosis of exclusion. Patients with a history of prolonged immobilisation presenting with hypercalcaemia should first have their serum calcium and albumin levels repeated. Once hypercalcaemia is confirmed, the investigations listed in Table 1 should be performed to better establish its aetiology.

Hypercalcaemia of immobilisation is characterised by the presence of:

- An appropriately suppressed parathyroid hormone level
- A suppressed parathyroid hormone-related peptide level
- A low 25-hydroxyvitamin D and a low 1,25-dihydroxyvitamin D level
- Hypercalciuria
- Elevated levels of cross-linked N-telopeptide of type 1 collagen
- Elevated levels of cross-linked C-telopeptide of type 1 collagen
- Low–normal bone-specific alkaline phosphatase levels
- Absence of other causes of non-parathyroid hormone-mediated hypercalcaemia.

The imbalance between bone formation and resorption is clearly outlined by measuring alkaline phosphatase, cross-linked N-telopeptide of type 1 collagen and cross-linked C-telopeptide of type 1 collagen. The low concentration of bone-specific alkaline phosphatase and raised levels of markers of bone resorption highlight how the rate of bone resorption exceeds that of bone formation (Malberti, 2013; Cano-Torres et al, 2016; Tettero et al, 2021).

The presence of non-parathyroid hormone-mediated hypercalcaemia in a patient with a history of prolonged immobilisation may suggest hypercalcaemia of immobilisation. However, there are various more common causes of non-parathyroid hormone-mediated hypercalcaemia that need to be excluded before entertaining the diagnosis of immobilisation hypercalcaemia, as summarised in Table 2 (Malberti, 2013).

Management

The management of immobility hypercalcaemia mainly involves enhancing renal excretion of calcium and inhibiting osteoclastic bone resorption.

Table 1. Suggested work up for hypercalcaemia in an immobile patient

Parathyroid hormone
Parathyroid hormone-related peptide
25-hydroxyvitamin D
1,25-dihydroxyvitamin D
Serum creatinine
Serum phosphate
24-hour urine calcium and creatinine
Bone-specific alkaline phosphatase
Serum cross-linked C-telopeptide of type 1 collagen
Serum cross-linked N-telopeptide of type 1 collagen

Table 2. Causes of non-parathyroid hormone-mediated hypercalcaemia
Malignancy
Haematological conditions
Granulomatous disorders
Medications
Endocrinopathies
Vitamin A or D intoxication

Immobility hypercalcaemia is cured by mobilisation. Passive movements and early weight-bearing rehabilitation exercises are essential to prevent and limit the above-mentioned pathophysiological processes. However, not all patients are safe to undergo early mobilisation and, in such cases, pharmacological management may be necessary (Labossiere et al, 2009).

One initial intervention in patients presenting with hypercalcaemia is fluid resuscitation with isotonic saline. This will correct the possible volume depletion associated with hypercalcaemia-induced salt-wasting. By expanding the intravascular volume, isotonic saline leads to an increased glomerular filtration rate, thus encouraging urinary calcium excretion partly as a result of reduced calcium reabsorption via the proximal tubule (Bilezikian, 2015).

Furthermore, since calcium excretion is a sodium-dependent process, giving isotonic saline presents more sodium and water to the distal convoluted tubule, thus promoting further calciuresis (Bilezikian, 2015; Turner et al, 2018).

Intravenous hydration with saline decreases serum calcium to safer levels, but less than 30% of patients achieve normocalcaemia with fluids alone (Crowley and Gittoes, 2013). Hence, this is usually only a temporary measure and more permanent remedies are commonly required to correct the hypercalcaemia.

Isotonic fluid administration requires careful monitoring. The Society for Endocrinology guideline on emergency management of acute hypercalcaemia in adult patients recommends monitoring for fluid overload in elderly patients and those with renal impairment (Walsh et al, 2016). Fluid overload can significantly worsen lung function, and in such instances, intravenous loop diuretics are advised (Walsh et al, 2016; Gittoes et al, 2020).

As previously described, enhanced bone resorption is the cause of immobilisation hypercalcaemia, so inhibiting this process should improve the serum calcium level. Therefore, intravenous bisphosphonates, which act by inhibiting osteoclast-mediated bone resorption, are important for controlling immobilisation hypercalcaemia in the long term. They are osteotropic substances with a high affinity for bone mineral as they bind to hydroxyapatite crystals especially at sites of active bone remodelling (Drake et al, 2008).

Non-nitrogen-containing bisphosphonates are structurally similar to pyrophosphate. They are thus easily incorporated into newly-formed intracellular molecules of adenosine triphosphate (ATP), inhibiting multiple ATP-mediated processes leading to cell apoptosis. The newer nitrogen-containing bisphosphonates act to inhibit farnesyl pyrophosphate synthase once they are internalised by osteoclasts. This enzyme forms part of the mevalonate pathway and its inhibition disrupts prenylation (lipid modification) of key signalling molecules in osteoclasts. As a result, the osteoclast develops cytoskeletal abnormalities that interfere with its ability to adhere to the bone surface and with its survival (Drake et al, 2008).

Intravenous zoledronic acid and pamidronate are the most commonly used bisphosphonates (Malberti, 2013). Zoledronic acid is more potent than pamidronate (Major et al, 2001). In fact, zoledronic acid is currently the first-line treatment for hypercalcaemia of malignancy (Chakhtoura and El-Hajj Fuleihan, 2021). This is relevant as both hypercalcaemia of malignancy and immobility hypercalcaemia are associated with enhanced bone resorption, albeit through different pathophysiological mechanisms (Major et al, 2001; de Beus and Boer, 2012).

Bisphosphonates are renally excreted and can cause acute or chronic kidney disease (Malberti, 2013). Their use is not recommended in patients with a creatinine clearance of less than 30–35 ml/min (Miller et al, 2013). Thus, the management of patients with immobility hypercalcaemia and severe chronic renal impairment can be challenging as bisphosphonates cannot be used safely.

In such cases, several case reports have revealed that denosumab may play a role in this subset of patients. Denosumab is a fully human monoclonal antibody that binds with high affinity to RANKL, preventing RANKL from interacting with its receptor (Uehara et al, 2017). Denosumab is currently indicated for:

- The prevention of skeletal-related events in adults with advanced malignancies involving bone (Amgen Limited, 2021)
- The treatment of osteoporosis in post-menopausal women and in men at increased risk of fractures (Amgen Limited, 2022)
- The treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (Amgen Limited, 2021).

Thus denosumab is currently registered for the treatment of hypercalcaemia of malignancy as part of skeletal-related events. The recommended dose of denosumab for treating hypercalcaemia of malignancy is 120 mg by subcutaneous injection every 4 weeks (Malberti, 2013; Amgen Limited, 2021).

As previously described, immobilisation is associated with a high RANKL:osteoprotegerin ratio which promotes bone resorption. Thus by inhibiting RANKL, denosumab may be a potential alternative yet off-label treatment to bisphosphonates for immobility hypercalcaemia in patients with renal insufficiency or in cases of bisphosphonate intolerance or failure (de Beus and Boer, 2012).

Denosumab has been used successfully in a small number of case reports in patients with immobility hypercalcaemia. The regimen used was a single dose of 60 mg subcutaneously, and in most cases, this not only resolved the hypercalcaemia but also led to hypocalcaemia (de Beus and Boer, 2012; Malberti, 2013; Gandhi et al, 2021).

Patients with hypovitaminosis D and chronic kidney disease have a greater risk of hypocalcaemia following denosumab administration. In such patients, administration of vitamin D and calcium is important to prevent this adverse event (Uehara et al, 2017).

Gittoes et al (2020) suggested that the risk of developing hypocalcaemia after receiving denosumab may be mitigated by vitamin D supplementation in patients with confirmed hypovitaminosis D or those suspected to have hypovitaminosis D and rebound hypocalcaemia. However, in the context of immobility hypercalcaemia, there is insufficient data on when to start calcium supplements, as in most cases, supplementation with calcium was commenced with the onset of hypocalcaemia (de Beus and Boer, 2012; Uehara et al, 2017). de Beus and Boer (2012) also suggested that a lower initial dose of denosumab may be used in such cases to prevent development of hypocalcaemia, but further studies are required.

Conclusions

Immobilisation is an uncommon cause of hypercalcaemia. It is characterised by a suppressed level of parathyroid hormone, low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels, hypercalciuria, and the presence of low–normal bone-specific alkaline phosphatase levels and increased cross-linked N-telopeptide and C-telopeptide of type 1 collagen. Hypercalcaemia of immobilisation is a diagnosis of exclusion, so other more common causes of parathyroid hormone-independent hypercalcaemia need to be ruled out before a patient is diagnosed with this condition. Management of immobilisation hypercalcaemia involves early initiation of mobilisation (passive and/or active) and rehabilitation, together with intravenous isotonic saline, calcitonin and bisphosphonates. Although not licenced for immobilisation hypercalcaemia, several case reports have also documented the successful use of denosumab for patients with immobility hypercalcaemia and renal insufficiency or immobilisation-related hypercalcaemia resistant to bisphosphonates. However, further studies are required to establish the optimal and safest management of immobilisation hypercalcaemia in this subset of patients.

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Learning points

- Immobilisation is a rare cause of parathyroid hormone-independent hypercalcaemia.
- Hypercalcaemia of immobility occurs as a result of an imbalance of bone remodelling, with osteoclastic bone resorption exceeding the rate of osteoblastic bone formation.
- Immobilisation hypercalcaemia is a diagnosis of exclusion.
- Management of immobilisation hypercalcaemia revolves around early mobilisation and rehabilitation, intravenous isotonic saline and bisphosphonates. Denosumab may be a potential alternative yet off-label option to bisphosphonates in patients with renal insufficiency.
- Greater awareness among physicians regarding immobilisation hypercalcaemia may help to prevent unnecessary and invasive investigations when a cause for parathyroid hormone-independent hypercalcaemia cannot be established in the immobile patient.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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