PRIMEVIEW

HYPOPARATHYROIDISM

nature REVIEWS DISEASE PRIMERS

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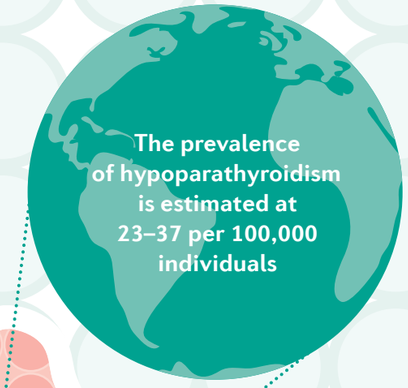
Hypoparathyroidism is characterized by inadequately low circulating levels of parathyroid hormone (PTH), which causes hypocalcaemia and hyperphosphataemia. The main clinical symptoms, such as tingling, muscle cramps and seizures, are the result of increased neuromuscular irritability.

EPIDEMIOLOGY

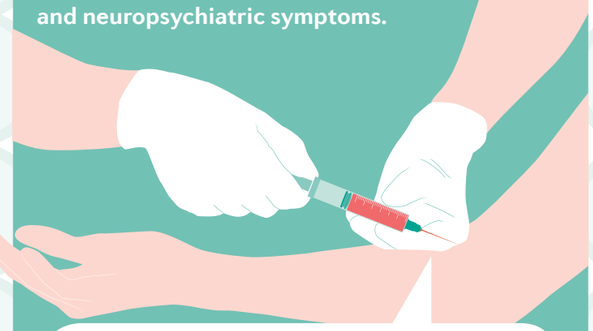
The most common cause of hypoparathyroidism is inadvertent removal of or injury to the parathyroid glands during neck surgery, for example, when performing thyroidectomy or radical neck dissection for malignancies



The prevalence of hypoparathyroidism is estimated at 23–37 per 100,000 individuals

DIAGNOSIS

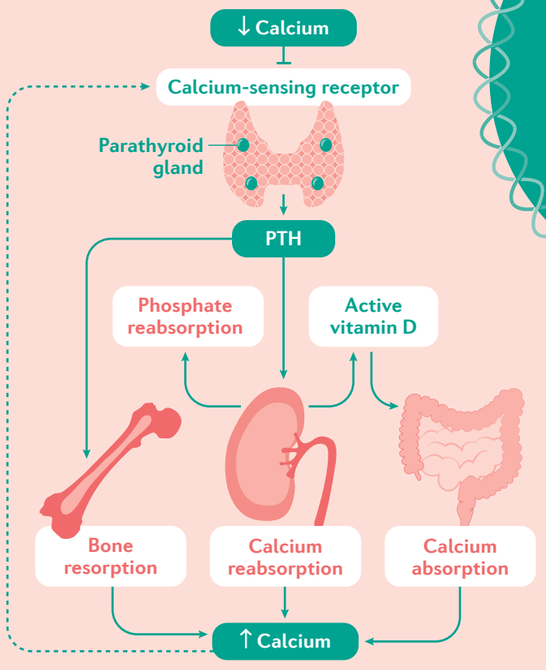
The clinical manifestations of hypoparathyroidism are variable. The disorder classically presents with neuromuscular irritability, which is the consequence of hypocalcaemia. Other manifestations include extraskeletal calcification (including in the brain and kidneys) and cardiovascular, musculoskeletal, ophthalmological, dermatological and neuropsychiatric symptoms.



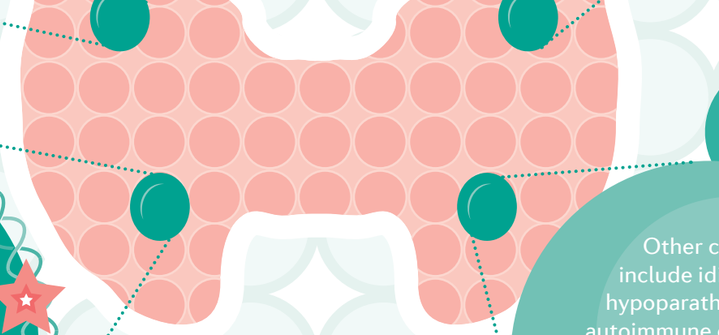
The combination of low calcium and absent, low or inappropriately normal PTH levels, given the hypocalcaemia, is the hallmark of hypoparathyroidism

MECHANISMS

A drop in serum calcium levels reduces the activation of the calcium-sensing receptor, which induces PTH release from the parathyroid glands. PTH stimulates bone resorption and increases calcium reabsorption and vitamin D activation in the kidney; vitamin D in turn induces intestinal calcium absorption. All of these mechanisms lead to an increase in serum calcium levels. PTH signalling in the kidney also inhibits phosphate reabsorption. Thus, hypoparathyroidism is associated with hypocalcaemia and hyperphosphataemia.



Mutations in genes involved in parathyroid gland development or function can cause hypoparathyroidism in <10% of cases (more commonly in children), and present as an isolated endocrinopathy, syndrome (for example, DiGeorge syndrome) or autosomal dominant hypocalcaemia



Other causes include idiopathic hypoparathyroidism, autoimmune destruction of the parathyroid glands or, very rarely, infiltrative diseases such as haemochromatosis, Wilson disease and metastatic cancer

MANAGEMENT

Conventional treatment with activated vitamin D and/or calcium supplements is the standard of care. Although this treatment can restore serum calcium levels, it cannot fully replace PTH and is associated with adverse events, such as an increased risk of developing kidney stones due to increased renal calcium excretion. PTH replacement has emerged as a new treatment option. Full-length rhPTH(1–84) has been shown to be safe and effective in studies lasting up to 6 years and has been approved in the United States and Europe as an adjunct therapy for adults who are not well-controlled on conventional therapy.

OUTLOOK

The lack of PTH can lead to hypercalciuria, even when serum calcium levels are controlled with conventional therapy. Although treatment with full-length recombinant human PTH (rhPTH(1–84)) has the potential to reduce urinary calcium excretion, data on the efficacy in preventing long-term complications are sparse, and safety data in large cohorts of patients, especially in children, are missing. The cost of and compliance to rhPTH(1–84) treatment are potential hurdles. Long-term, multicentre controlled trials in adults and children are necessary to determine the best possible treatment of hypoparathyroidism.

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