



Secondary hyperparathyroidism and immune system in chronic kidney disease patients

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Parathormone receptors are located on various immune cells and various studies support the possibility that parathormone affects the immune system, however, further research is required, particularly since this abnormality could be reversed with the treatment of secondary hyperparathyroidism in uremic patients. Secondary hyperparathyroidism in end-stage kidney disease patients has been found as a possible factor in the development of an acquired immune dysfunction (1-3). In fact, high levels of parathormone have been found in various complications associated with uremia. In general, hypocalcemia, decreased calcitriol production and hyperphosphatemia, may all increase the parathormone production and hyperplasia of parathyroid cells, ultimately resulting in secondary hyperparathyroidism. Secondary hyperparathyroidism develops frequently in chronic renal failure as an adaptive response to deteriorating renal function (2-6). A mixture of various factors related to the raise of parathormone that are additive. Parathormone is an 84-amino acid polypeptide secreted by the parathyroid gland. The homeostasis of this hormone, is mainly controlled by calcium/phosphorus and vitamin D regulation. Circulating 1,25-dihydroxy vitamin D starts to reduce very early in stage 2 of chronic renal failure and continues to decrease as the glomerular filtration rate decreases more, and the kidney 1 α -hydroxylase is inhibited by hyperphosphatemia, metabolic acidosis, hyperuricemia, and also 25-hydroxyvitamin D deficiency (1-7). Parathormone adversely influences the metabolism of various cells and organs. It causes metabolic bone disease, cardiac arrhythmias, peripheral neuropathy and importantly anemia through inhibiting precursors of erythropoiesis and also glucose intolerance (4-7). The parathyroid gland implies a central role in the regulation of mineral metabolism. In patients with chronic kidney disease, circulating levels of parathormone are progressively increased as renal function diminishes. In

■ Implication for health policy/practice/research/medical education

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addition to a phosphate retention, decreased production of 1,25-dihydroxyvitamin D and hypocalcemia, the identification of fibroblast growth factor 23 and its related cofactor Klotho offers significant implications for the deeper appreciation of disordered mineral metabolism in chronic renal failure (3-8). In early stages chronic renal failure, increased fibroblast growth factor 23 to maintain neutral phosphate balance results in suppression of kidney 1,25(OH)₂D production and thus triggers the early development of secondary hyperparathyroidism too. As glomerular filtration rate decreases under 60 ml/min, phosphate is retained and stimulates synthesis and secretion of parathormone. Additionally, hypocalcaemia develops as the glomerular filtration rate decreases below 50 ml/min, further stimulating release of parathormone (4-8). With disease development, intact parathormone half-life increases and C-terminal fragments of the hormone accumulate. Hence a relative state of end-organ resistance to the parathormone exists, however chronic elevation of it has major consequences leading in bone loss (mainly cortical bone), vascular calcification, cardiovascular disease, fractures, and thus an increased cardiovascular mortality. While parathormone receptors were found on most immunologic cells, parathyroid hormone also functions as an immunologic mediator. It

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was found that, patients with more advanced stages of kidney disease are prone to oxidative stress. Consequently hormones like parathormone are oxidized (1-4,6-8). The oxidized parathormone may lose its biological activity by losing its ability to interact properly with their receptors. Parathormone has two methionine residues at position 8 and 18 and various investigations have shown that oxidation of parathormone abolish its interaction with its receptor. Oxidized parathormone does not stimulate the parathormone receptor to generate cAMP, and is therefore most likely biological inactive. Thus oxidized parathormone loses its biological properties. Recent studies showed that parathormone produces an inhibitory effect on some parameters of the immune system, however, other investigations showed that parathormone had a stimulatory function under certain laboratory situations. More recent studies have shown that, different cytokines have osteoclasts as a target site. These cytokines influenced bone remodeling by activating a parathormone receptor on the monocyte-like precursor of osteoclasts. The mechanism by which parathormone affected leukocytes is ill-understood, since there seems to be an increase in intracellular calcium level. Potentially, this may lead to an increase in cellular adenylate cyclase activity (5-8). Finally, parathormone receptors are discovered on various immune cells and various investigations supports the possibility that parathormone influences the immune system, however, additional researches is required, mainly since this abnormality could be reversed with the treatment of secondary hyperparathyroidism in hemodialysis patients (7-10).

Authors' contributions

All authors wrote the manuscript equally.

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