Parathyroid hormone, glucose metabolism and diabetes mellitus

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The parathyroid glands secrete parathyroid hormone (PTH) in response to reduced calcium levels resulting in an increase in bone resorption and subsequently normalization of calcium levels. In vitamin D deficiency, secondary hyperparathyroidism leads to increased bone turnover and increased bone loss (1). PTH is a polypeptide containing 84 amino acids (2) that maintains the extracellular calcium levels within a narrow normal range and regulates plasma calcium homeostasis (3).

There are conflicting reports related to the role of PTH on glucose hemostasis. Limited studies suggest a role for this hormone in insulin sensitivity through its role in increases the production of 1,25-dihydroxyvitamin D [1,25(OH)2D] (4). Animal studies indicated that, in 1,25(OH)2D-deficient rats, the insulin synthesis and release decreased in islet cells, and following treatment of rats with 1,25(OH)2D the function of insulin secretion of the beta cells is restored (4). However, most studies suggest that high level of PTH is associated with abnormal glucose metabolism and is related with the prevalence of diabetes mellitus. Both primary and secondary hyperparathyroidism are involved in abnormal glucose metabolism. There is higher prevalence of diabetes mellitus in patients with primary hyperparathyroidism (5), while removing parathyroid glands improve glucose tolerance in these individuals (6). Diabetes mellitus is more prevalent in patients with high levels of PTH by two to four times. Epidemiological studies demonstrated that serum level of PTH was positively and negatively associated with glucose level and insulin sensitivity, respectively. The relationship between PTH and insulin resistance is also supported by intervention studies as parathyroidectomy, and a reduction in serum PTH concentration in patients with high levels of PTH, normalizes blood glucose levels. Furthermore, when exogenous PTH is administered to laboratory animals there is an increase in plasma glucose concentrations. These observations suggest that PTH may interfere with either the ability of the pancreas to release insulin, the actions of insulin on glucose metabolism, or both. Association between serum PTH levels and abnormal glucose metabolism or diabetes has been supported through inhibition of insulin signaling in adipocytes by PTH. PTH through binding to a G-protein coupled receptor stimulates, adenylate cyclase enzyme that increases the production of cAMP. Increased level of cAMP through activation of protein kinases results in phosphorylation of insulin receptor substrate 1 (IRS-1) on serine 307. Reduction of expression of IRS-1 and glucose transporter 4 (GLUT4) and decreases in insulin-induced glucose transport explains an association between high serum levels of PTH and insulin resistance and incidence of diabetes (2). Furthermore, It has been demonstrated that plasma intact PTH level is inversely correlated with insulin sensitivity index in healthy subjects that could support the role of hyperparathyroidism in the pathogenesis of diabetes mellitus (7).

In obese girls, PTH and PTH/25-OHD were negatively associated with homeostasis model assessment of insulin resistance (HOMA-IR) (4). An inverse relationship between PTH or PTH/25-OHD with insulin resistance measures might be due to PTH-suppressive effects of insulin (4). Low serum levels of calcium and 25 (OH) D along with elevated level of PTH have been demonstrated in type 1 diabetes mellitus (T1DM) patients (6). New onset diabetes mellitus is occurred after renal transplantation. An association between this condition and higher PTH level has recently been reported through suppression of insulin signal transduction in adipocytes that resulted in insulin resistance (5).

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News and Views

Implication for health policy/practice/research/medical education

Both primary and secondary hyperparathyroidism are involved in abnormal glucose metabolism. There is higher prevalence of diabetes mellitus in patients with primary hyperparathyroidism, while removing parathyroid glands improve glucose tolerance in these individuals.
Finally, the presence of metabolic syndrome is associated with higher risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease. It has been suggested that lowering PTH through medication, higher intake of calcium and vitamin D or weight reduction decreases the risk of metabolic syndrome in women (8). In obese adolescents, metabolic syndrome is associated with a higher intact PTH:25 (OH) D ratio than those without a metabolic syndrome (9).

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**References**

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