Parathyroid Glands

The four parathyroid glands, derived from pharyngeal pouches III and IV, are found on the surface of the thyroid gland and consist of chief cells and oxyphilic cells. The glands generally derive their blood supply from a single artery, most often the inferior thyroid artery, although anastamoses do exist between the glands and adjacent structures.

Triggered by low ionized calcium levels, the gland releases parathyroid hormone from chief cells, which acts on bone, kidney and intestine to increase calcium levels in the body. Calcium-sensing receptors inhibit the release of parathyroid hormone (PTH) when serum calcium levels are elevated; point mutations of the gene coding for this receptor result in familial hypocalciuric hypercalcemia. PTH works directly on bone and kidney, increasing mineral dissolution in bone and reabsorbing more calcium in the kidney while concurrently decreasing the reabsorption of phosphorus. In the kidneys, the hormone also increases the level of active vitamin D produced. This provides PTH’s indirect effect on the gut as activated vitamin D increases the amount of calcium absorbed from the intestinal lumen.

PTH binds to the PTH/PTHrP receptor, stimulating different signaling pathways depending on the tissue involved. Parathyroid hormone-related peptide (PTHrP), a hormone whose functions have not fully been elucidated, is necessary for bone development in the fetus and has paracrine actions within adult tissue. It binds to the same receptor as PTH and is important in the pathophysiology of hypercalcemia due to malignancy. Since the kidneys metabolize PTH, renal insufficiency can cause accumulation of the hormone.

The effects of PTH are countered to a limited extent by calcitonin, released by the parafollicular cells of the thyroid. Counterintuitively, osteoblasts rather than osteoclasts possess PTH receptors; the osteoblasts then release cytokines, which activate osteoclasts to increase bone remodeling.

PTH excess over an extended period of time has deleterious effects on bone density; some of the changes induced by PTH on bone include an increase in the number of osteoclasts and osteoblasts. While hyperparathyroid patients in the past would present with “stones, bones, groans and moans,” improvements in screening assays for calcium and parathyroid levels have led to more patients presenting asymptotically and without overt clinical signs of disease. Hypercalcemia most often arises from primary hyperparathyroidism, a common condition that occurs more often in women. Hyperparathyroidism has several causes, including PTH-releasing adenomas, hyperplasia of the gland and (rarely) parathyroid carcinoma. Parathyroid neoplasms, similar to thyroid cancer, may arise in patients with a history of ionizing radiation exposure. Malignancies in other parts of the body may produce PTHrP, also leading to hypercalcemia by activating the PTH receptor. PTHrP eludes available assays for PTH; it is detected via different tests. Additionally, parathyroid hyperplasia may develop in patients...
with MEN I or MEN IIa. Treatment of primary hyperparathyroidism is somewhat controversial in asymptomatic patients. While it is clear that surgery is the treatment of choice for younger patients and for those with symptoms, many also advocate parathyroidectomy in asymptomatic patients as well in order to avoid the long-term sequelae of elevated PTH and because many patients experience disease progression. Medical management of hyperparathyroidism has not been thoroughly studied, however, low bone density can be combated with a variety of drugs, including estrogen, SERMs and bisphosphonates. Even PTH, administered in periodic doses rather than the persistent elevation seen in hyperparathyroidism, induces increased bone formation rather than its breakdown.

Parathyroid neoplasms are also treated surgically. Ultrasonography and sestamibi scans localize the tumor pre-operatively, while radio-guided, endoscopic or video-assisted localization are minimally invasive techniques that may shorten the duration and invasiveness of the subsequent parathyroidectomy; these techniques are no longer in favor for use during a parathyroidectomy. It should be noted that these scanning techniques are most accurate when a single nodule is responsible; multiglandular disease cannot be treated with minimally invasive techniques. Intra-operative parathyroid hormone assays also contribute to a surgeon’s success.

Differentiating between an adenoma and carcinoma can prove difficult as the lesions often resemble each other. However, only carcinoma will metastasize and invade; carcinomas also present with more mitotic figures, as well as nuclear atypia and desmoplastic reactions.

Conditions involving a deficiency of parathyroid hormone include hypoparathyroidism, pseudohypoparathyroidism and pseudopseudohypoparathyroidism. Hypoparathyroidism, while uncommon, most often occurs as a complication of thyroidectomy; other causes of hypoparathyroidism exist, but are even less common. Transient hypoparathyroidism after surgery may occur and resolve in the weeks after the procedure; hypoparathyroidism persisting for six months or longer is designated as chronic. Signs of hypoparathyroidism are those of hypocalcemia: low serum calcium and high phosphate, tetany, hyporeflexia, paresthesias, anxiety, convulsions, among others. Vitamin D is given therapeutically to treat chronic hypoparathyroidism, but can be difficult to dose due to the risk of developing Vitamin D intoxication.

Pseudohypoparathyroidism occurs when the PTH receptor does not recognize PTH. This usually affects the renal receptors, not those in bone. The congenital defect may be in the receptor, in a G protein associated with the receptor, or in adenyl cyclase; the different subtypes account for each mutations. The disease can manifest in a characteristic phenotype including a short stature, round face, obesity, mental retardation and the “knuckle knuckle dimple dimple” sign. Pseudo-pseudohypoparathyroidism describes patients who phenotypically resemble pseudohypoparathyroid patients but have normal calcium levels.
References:

