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Secondary and Tertiary Hyperparathyroidism: When to Operate and When Not to!

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INTRODUCTION Chronic kidney disease-mineral and bone disease is a systemic disorder which is manifested by laboratory abnormalities of calcium, phosphorus or calcitropic hormones. It also involves the abnormalities in bone turnover, mineralization, volume, linear growth, vascular or soft tissue calcification. Secondary hyperparathyroidism is defined as adaptive parathyroid gland hyperplasia and increased production of PTH. Tertiary hyperparathyroidism is severe, persistent, and progressive elevation of serum parathyroid hormone (PTH) that cannot be treated adequately by medical therapy (including both vitamin D analogs and calcimimetics) without causing significant hyperphosphatemia or hypercalcemia.

KEYWORDS Secondary Hyperparathyroidism, Tertiary Hyperparathyroidism, Surgery

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Review Article

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Chronic kidney disease-mineral bone disease is a systemic disorder which can lead to abnormal levels of calcium, phosphorus and parathyroid hormone. It can affect the bone mineralization and bone growth. It can also result in vascular and soft tissue calcification. Parathyroid hormone level starts increasing with progression of chronic kidney disease and decline in eGFR around 45 mL/min per 1.73 m^2 or lower. Almost all the dialysis patients have secondary hyperparathyroidism which is an enlargement of parathyroid gland and increased production of parathyroid hormone. Persistently elevated parathyroid hormone despite the medical therapy with vitamin D analogs and calcimimetics is defined as tertiary hyperparathyroidism.

EPIDEMIOLOGY

The prevalence of refractory hyperparathyroidism is estimated by the rate of parathyroidectomy. It is less common in non-dialysis patients. Among dialysis patient, the rate of parathyroidectomy for refractory hyperparathyroidism is approximately 7-10 per 1000 patient-years[1].

PATHOPHYSIOLOGY

The pathophysiology of secondary hyperparathyroidism involves several organs like kidneys, parathyroid glands, bones, intestines and the vasculature. Parathyroid gland has calcium sensing receptors and vitamin-D receptors. Series of abnormalities occur with the progression of kidney disease. Circulating fibroblast growth factor-23(FGF-23) increases early in chronic kidney disease and suppresses 1 alpha hydroxylase in the kidney leading to deficiency of 1,25-dihydroxy vitamin D. Vitamin D deficiency results in hypocalcemia which stimulates parathyroid hormone secretion. Phosphate retention causes hypocalcemia and also directly stimulates PTH secretion[2]. Elevated PTH in return causes bone resorption and calcium mobilization to maintain calcium homeostasis. In tertiary hyperparathyroidism, there is a decreased expression of calcium sensing receptors and vitamin D receptors, resulting in lack of suppression of PTH. Thus hyperparathyroidism is refractory to medical therapies such as vitamin D analogs and calcimimetics. The persistent stimulation of parathyroid cell growth results in renal osteodystrophy, nodular hyperplasia of parathyroid gland, and sometimes parathyroid adenoma.

CLINICAL FEATURES

The patients with secondary and tertiary hyperparathyroidism can present with hypercalcemia, hyperphosphatemia, bone pain, fractures, proximal muscle weakness, vascular calcification, pruritus and calciphylaxis.

Renal Osteodystrophy

The major bony lesions involved in renal osteodystrophy are osteitis fibrosa (increased remodeling-resorption), adynamic bone disease (no remodeling, hypocellular bone), osteomalacia (defective mineralization due to aluminum deposition), and mixed uremic osteodystrophy involves

both, high turnover with mineralization defects[3]. Patients with renal osteodystrophy are at increased risk of bone fractures as compared to general population due to change in quality of bone. It is more common in dialysis patients.

Calciphylaxis

Hyperparathyroidism, hyperphosphatemia and increased plasma calcium x phosphate product is associated with soft tissue and vascular calcification. Secondary hyperparathyroidism is associated with higher levels of circulating alkaline phosphatase in dialysis patients and it is stronger predictor of coronary artery calcification in dialysis population[4]. Other risk factors include vitamin D analogs, calcium based binders, female gender, obesity and diabetes. Biopsy is needed to confirm the diagnosis. Calciphylaxis or calcific uremic arteriole apparently is associated with poor prognosis.

Resistant Anemia

Parathyroid hormone may be directly toxic to bone marrow erythroid progenitors resulting in increased hemolysis and may also be associated with bone marrow fibrosis. This results in failure to achieve target hemoglobin in spite of adequate iron stores.

PHARMACOLOGICAL MANAGEMENT OF SECONDARY AND TERTIARY HYPERPARATHYROIDISM

Vitamin D therapy: Vitamin D analogs and calcitriol are effective in reducing the level of parathyroid hormone in chronic kidney disease. These are widely used in dialysis population. The excessive use of vitamin D analogs is associated with increased risk of hypercalcemia and hypophosphatemia promoting vascular calcification.

Calcimimetics: Calcimimetics increase the sensitivity of calcium sensing receptor in parathyroid gland to circulating calcium. These agents in combination with vitamin D analogs often lower serum calcium and phosphorus in dialysis patients. Their role to decrease the mortality, cardiovascular events or fracture rate remains controversial. The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events trial evaluated cinacalcet versus placebo in 3883 patients on hemodialysis and noted a nonsignificant reduction in the primary composite end point of all-cause mortality, nonfatal myocardial infarction, hospitalization for unstable angina, congestive heart failure, and peripheral vascular events .

Phosphorus binders: Phosphorus retention in chronic kidney disease is an important factor in pathogenesis of early secondary hyperparathyroidism. Hyperphosphatemia can also be a consequence of secondary hyperparathyroidism. Calcium based phosphorus binders increased risk of hypercalcemia and vascular calcification. Calcium free binders such as sevelamer and lanthanum carbonate or iron based binders may be less associated with arterial calcification. Survival benefit from use of phosphorus binders is unclear[5].

SURGICAL MANAGEMENT

Parathyroidectomy is indicated in patients with hyperparathyroidism that is refractory to medical therapy like vitamin D analogs and calcimimetics. It is usually required in about 15% of patients after 10 years and 38% of patients after 20 years of dialysis therapy[6].

Parathyroidectomy is indicated for persistently elevated PTH level (generally greater than 800-1000 pg/mL) for more than 6 months despite optimized pharmacological therapy including vitamin D analogs and calcimimetics. Improved survival with parathyroidectomy noted from observational studies especially in case of nodular parathyroid hyperplasia. Other indications include 1) refractory hypercalcemia (corrected calcium >10.2 mg/dL) and refractory hypophosphatemia (phosphorus >5.5 mg/dL) in spite of dietary compliance and maximized pharmacological treatment, 2) increased risk or presence of vascular and soft tissue calcification, 3) calciphylaxis, 4) anemia resistant to erythropoietin therapy despite adequate iron stores. Parathyroid ultrasound and 99mTc-sestamibi scan may help to reduce the risk of recurrent disease by detection of ectopic thyroid tissue and identifying which parathyroid has lowest sestamibi uptake and can be used as a remnant tissue. Hyperparathyroidism resolves in most patients after renal transplantation however may need parathyroidectomy in patients with severe refractory hyperparathyroidism with moderate to severe symptoms. Persistent hyperparathyroidism and hypercalcemia have been associated with decreased graft function.

Surgical options: Dialysis patients with secondary and tertiary hyperparathyroidism usually have multiple enlarged parathyroid glands. Surgical options are total versus subtotal parathyroidectomy. Surgical outcomes among both options are about the same. Subtotal parathyroidectomy carries low risk of postoperative hypocalcemia as it reserves remnant parathyroid tissue with its original blood supply. This option is preferred when there is only single or double parathyroid adenoma whereas total parathyroidectomy with auto-transplantation is preferred in patients with several comorbidities and reasons (like previous history of neck surgery, recurrent laryngeal nerve injury, poor functional status) to avoid reoperation.

Survival benefit after parathyroidectomy: There are no randomized clinical trials to evaluate the outcomes after parathyroidectomy however several observational studies have shown that parathyroidectomy is associated with

improved survival. In meta-analysis by Chen et al obtained from 13 cohort studies involving around 20,000 patients, out of which 10,000 had a parathyroidectomy and it was associated overall 28% decrease in all-cause mortality and 37 points reduction in cardiovascular mortality[7]. Parathyroidectomy can also improve many symptoms related to hyperparathyroidism like better control of serum calcium and phosphorus, reduced risk of fractures[8], increased bone mineral density and improvement in overall quality of life[9].

Limitations and complications: Adherence to medical treatment is important to be evaluated before surgical intervention. Parathyroidectomy is associated with significant postoperative morbidity and increased hospitalization. Some of the common symptoms in dialysis patient like pruritus, weakness and generalized pain may not improve even after surgery.

Hungry bone syndrome: Hungry bone syndrome is characterized by hypocalcemia, hypophosphatemia and hypokalemia due to abrupt bony uptake of calcium, phosphorus and magnesium into bone due to sudden drop in PTH levels after surgery. It often requires intravenous calcium replacement followed by higher doses of oral vitamin D and calcium supplementation[10].

When not to operate: Parathyroidectomy is contraindicated in patients with familial hypocalciuric hypercalcemia presenting with elevated calcium and PTH levels. Other contraindications include contralateral recurrent laryngeal nerve injury and vocal cord dysfunction.

CONCLUSION

Secondary hyperparathyroidism is common with the progression of chronic kidney disease. Pharmacological treatment includes administration of vitamin D analogs and calcimimetics. About 15% of dialysis patients will need parathyroidectomy. Based on the available observational data, parathyroidectomy is a reasonable choice in patients who are refractory to maximized pharmacological treatment.

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