



## Pancreatitis Associated with Parathyroidectomy

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### Abstract

Hyperparathyroidism (HPTH) has been recognized as a rare cause of pancreatitis. There may also be an association between surgery for hyperparathyroidism and the subsequent development of acute pancreatitis as well, but there is not a consensus in the published literature. We encountered a patient who developed acute pancreatitis immediately following parathyroidectomy, complicated by the development of a subsequent pancreatic pseudocyst. A subsequent review of one surgeon's experience with HPTH and pancreatitis over a ten year period revealed only this index case here presented out of a total of the 229 patients undergoing an operation for hyperparathyroidism (0.4% incidence). These findings and a thorough review of the current literature indicate that the relationship between parathyroidectomy and pancreatitis is limited to several case reports and the results of one prospective study that have not been replicated. However, an index of suspicion for the diagnosis of acute pancreatitis should be considered in those patients who may develop abdominal pain following parathyroidectomy for HPTH.

### Introduction

Primary hyperparathyroidism (HPTH) is a common endocrine disorder that has been accepted as a rare cause of both acute and chronic pancreatitis [1-5]. This association was studied as early as 1957 by Cope et al. who suggested that HPTH primarily caused pancreatitis secondary to elevated serum calcium [6]. Additional mechanisms have been discussed in the literature since those initial reports.

Parathyroidectomy as a precipitating factor in pancreatitis has been less well studied through case reports and few formal investigations [7-11]. The purpose of this report is to present the case of a patient who developed complicated pancreatitis immediately following parathyroidectomy and a review of one surgeon's experience with this occurrence, as well as to review the current body of literature on this topic.

### Background and Methods

One patient presented with acute pancreatitis within his first postoperative day following parathyroidectomy without any common risk factors associated with the disease. This prompted a review the literature on the topic of pancreatitis precipitated by surgery for HPTH. As the literature presented inconclusive results, one surgeon reviewed the occurrence in his own practice of surgically treated HPTH cases over a ten-year period. The data was analyzed only for the occurrence of pancreatitis in these patients with follow-up ranging 1 to 11 years post-operation. Pertinent laboratory values are presented for the index patient case but were not available for a large portion of the patients reviewed over the ten year period, and further detailed analysis was not within the scope of this study.

### Results

A 50-year-old presented to the emergency department (ED) on postoperative day one with chief complaint of epigastric abdominal pain radiating to the back with associated nausea. Medical history was significant for hyperparathyroidism with parathyroidectomy for removal of a 1.3 g adenoma measuring 3 × 1 × 0.3 cm. He had no prior history of pancreatitis or problems with abdominal pain. Medications were limited to 500 mg of calcium daily and 5 mg/325 mg of acetaminophen/oxycodone for pain control. The patient denied a history of tobacco use, noting only occasional alcohol use without any recent consumption. Family medical history was noncontributory.

On examination the patient had findings consistent with pancreatitis, particularly epigastric

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tenderness. Laboratory abnormalities included a white blood cell count of 17,000 with 82.3% segmented neutrophils, a lipase of 3079 U/L, a potassium level of 3.1 mEq/L, and an alkaline phosphatase of 159 U/L. The patient's serum calcium was 9.1 mg/dL, decreased from a preoperative level of 10.9 mg/dL. All other laboratory values including total bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT) were within normal limits. Computed tomography (CT) was performed with results demonstrating infiltrative findings in the peripancreatic fat planes consistent with pancreatitis.

After a three day hospitalization, the patient clinically improved and his laboratory values normalized. Due to the severity of his pancreatitis and some persistent abdominal pain, a follow up CT scan was performed outpatient. This showed the development of a 3 cm pseudocyst, which was followed conservatively with near complete resolution noted at 10 weeks on CT scan.

Because the patient's presentation was severe and temporally related to the previous surgery, his case prompted a review of the literature. A subsequent retrospective review of a single surgeon's parathyroidectomy cases over a span of ten years was also performed. This review identified 229 patients who underwent parathyroidectomy from 2006 to 2016. These cases were reviewed for the development of postoperative pancreatitis. Any patients presenting with abdominal pain from the time of the first postoperative visit were considered for possible parathyroidectomy-related pancreatitis. Of the 229 patient cases included in review, only one case (summarized above) presented with pancreatitis following surgery resulting in a 0.4% incidence.

## Discussion

Though the relationship between HPTH and pancreatitis has been established for some time, the prevalence of pancreatitis in these patients has been a point of debate. While some authors cite rates as high as 15%, others consider the association to be diminishingly rare [12,13]. The decreasing frequency of pancreatitis with regard to HPTH may be due to earlier treatment of parathyroid disease in the disease process and frequent monitoring of calcium levels as a part of basic blood work. The most recent report by Diallo sets forth a more modest incidence of 3.6%, significantly higher than the roughly 0.1% seen in the general population [3,14].

While this relationship is often considered causal based on several proposed mechanisms, some studies have provided results that create a more complicated picture. Cope et al. originally proposed that hypercalcemia resulting in the deposition of calcific calculi in the pancreatic ducts lead to the development of pancreatitis. Another suggested mechanism is the activation of trypsinogen to trypsin due to higher calcium serum levels [15]. In an earlier paper by the same authors, a hormonal mechanism based on glucagon activity on serum calcium was proposed to emphasize the reciprocal effects of pancreatic dysfunction as a cause of HPTH [16].

Recently, Felderbauer et al. [17] proposed a genetic basis for pancreatitis secondary to HPTH-induced hypercalcemia. Among the 826 patients prospectively studied, pancreatitis risk was elevated ten-fold in patients with HPTH. Using deoxyribonucleic acid (DNA) sequencing, the authors found that mutations in the serine protease inhibitor Kazal type I gene (N34S) were unique to patients with HPTH and pancreatitis. Finally, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene were detected only in patients with HPTH and pancreatitis.

It is important to note that several authors have failed to replicate this relationship between HPTH and pancreatitis in their own work. In one retrospective study of 684 patients, researchers found that there was no increased incidence of pancreatitis associated with those who met the criteria for HPTH [18]. Another review of 1,153 patients who underwent surgery at the Mayo Clinic for HPTH found the prevalence of pancreatitis to be 1.5%, which the authors considered approximate to the general occurrence in hospital populations [19]. Both studies concluded that the causal relationship between HPTH and pancreatitis was questionable at best.

One reason for the heterogeneity of the literature surrounding this question is the diversity in study design. Khoo considered only cases of acute pancreatitis; moreover, the cases had to meet two of the following criteria: pancreatic enzymes three times normal, a classical presentation of abdominal pain, and radiological evidence, which was not further defined. The work done by Bess. focused only on those HPTH patients who underwent parathyroidectomy at a specific institution. Other studies compared results from cohorts that were separated in time by decades, which reflects the epidemiologic changes in HPTH pancreatitis over the years but also provides a heterogeneous sample for investigation.

The idea of HPTH as an etiology of pancreatitis is lent additional support by several studies in which parathyroidectomy resulted in complete resolution of the patients' pancreatitis [12,20]. Resolution of pseudocysts following parathyroidectomy has also been observed.

Unexpectedly, it has also been suggested that parathyroid surgery may itself play a role in precipitating pancreatitis. One prospective study of 86 patients undergoing neck exploration for HPTH compared to 34 controls found a significantly higher incidence of hyperamylasemia in the surgical group; additionally, the rate of post-operative pancreatitis was observed to be about 9%. In those patients simultaneously undergoing thyroidectomy, the rates of hyperamylasemia and pancreatitis were even more elevated.

While no other authors have replicated this incidence at the 9% level, other reports have noted the development of pancreatitis following parathyroid surgery. According to Mjåland and Normann, the incidence of pancreatitis in these patients is closer to 1%, with a review of the literature revealing 31 cases in a sample of 2797 patients. Other authors have produced contradicting results through retrospective studies [11,21]. Our own finding of a 0.4% incidence of pancreatitis after parathyroidectomy falls below the figures presented by both the Reeve and Mjåland reports. Rather, it is comparable to the rates observed in the general population and general hospitalized population.

While it is challenging to account for these disparities, one weakness in these retrospective reports is the inability to accurately follow up on all patients who may have represented for pancreatitis or similar such symptoms following surgery. Our own data was limited by an inability to include any cases of pancreatitis that may have presented to outside institutions. Additionally, retrospectively reviewing surgical cases of HPTH likely introduces an unexplored selection bias.

Thought parathyroidectomy as a cause of pancreatitis is lacking solid support in the body of literature reviewed, several pathogenic mechanisms have been proposed. First mentioned by Reeve et al. but then discussed more recently is the idea that the calcitonin producing C-cells of the thyroid are less productive in states of

hypercalcemia that would normally stimulate hormone production. This “calcitonin fatigue” is supported by the increased incidence of pancreatitis observed in patients undergoing neck dissection with both thyroidectomy and parathyroidectomy as compared to the parathyroidectomy alone.

In a report by Klepsch and Bergenfelz, the authors hypothesize that this postoperative pancreatitis results from rapid reduction of serum calcium. To prevent such a sharp reduction, the patient was prophylactically treated by an infusion of calcium dosed 12 g/24h, which itself was unlikely to have precipitated the pancreatitis as the patient’s serum calcium levels never increased. Mjäländ and Normann suggest that this post-operative pancreatitis is also related to severity of the preceding disease as their patient was measured to have the highest parathormone and calcium levels on their records; however, more data is required to comment of this finding.

## Conclusion

Hyperparathyroidism (HPTH) is a rare cause of pancreatitis with changing epidemiology as the management of HPTH continues to evolve. Parathyroidectomy has been proposed as another potential cause of pancreatitis, but the relationship between these two entities remains questionable with support limited largely to one prospective study and case reports. Additionally, the data presented shows a rate comparable to the incidence of pancreatitis observed in the general population. Though the current literature does not provide evidence to support a causal relationship between these two entities, patients developing abdominal pain following parathyroidectomy may have a potentially severe, associated pancreatitis, and an index of suspicion should be maintained to ensure accurate and timely diagnosis.

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