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ORIGINAL ARTICLE

DOES HYPERPARATHYROIDISM CAUSE PANCREATITIS? A SOUTH INDIAN EXPERIENCE AND A REVIEW OF PUBLISHED WORK

JUBBIN J. JACOB,* MATHEW JOHN,* NIHAL THOMAS,* ASHOK CHACKO,† REKHA CHERIAN,‡ BEN SELVAN,§ ARAVINDAN NAIR§ AND MANDALAM S. SESHADRI*

**Departments of Endocrinology, ‡Radiology, §Surgical Endocrinology and †Gastroentrology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India*

Background: The association between pancreatic disease and primary hyperparathyroidism (PHPT) is controversial. We attempt to suggest a causal correlation and characterize the nature of pancreatic disease in PHPT.

Methods: This study is a retrospective review of the medical records of patients who were diagnosed with PHPT and presented with pancreatic disease between 1 May 2000 and 30 May 2005 at Christian Medical College, Vellore.

Results: During the period of 5 years, there were 1284 patients with pancreatic disease and 101 patients with PHPT admitted to our hospital, accounting for 0.42 and 0.03%, respectively, of the total hospital inpatient admissions of 302 883. Of them, 13 patients had both pancreatic disease and PHPT accounting for 1% of all admissions for pancreatic disease and 12% of admissions for PHPT. Patients admitted with PHPT have a 28-fold increased risk of developing pancreatitis compared with patients admitted without parathyroid disease. The ages of the patients ranged from 22 to 52 years with a median age of 37 years. There were 9 male and 4 female patients. The mean calcium values among patients with PHPT and pancreatic disease were significantly higher than patients with PHPT without pancreatic involvement.

Conclusion: The data suggest a causal association between the pancreatic disease and PHPT. This may be correlated to the higher calcium values. Until more information is available, it would be prudent to check serum calcium in all patients presenting with unexplained pancreatic disease.

Key words: hypercalcaemia, pancreatic disease, pancreatitis, primary hyperparathyroidism.

Abbreviations: iPTH, intact parathyroid hormone levels; OFC, osteitis fibrosa cystica; PHPT, primary hyperparathyroidism; SAP, serum alkaline phosphate; TCP, tropical chronic pancreatitis.

INTRODUCTION

Despite numerous case reports linking hyperparathyroidism with pancreatic disease there seems to be a paucity of information regarding the clinical characteristics of pancreatic disease in hyperparathyroidism. The initial description of the association was described as early as 1940 when Smith and Cooke described a patient who succumbed to acute pancreatitis correlated to hyperparathyroidism.[1] In 1962 Mixter *et al.* reported 62 cases of pancreatitis occurring in association with primary hyperparathyroidism (PHPT) after reviewing the published work.[2] Subsequent reports have focused on the development of pancreatitis in patients who are operated on for hyperparathyroidism.[3–5] The contradictory point was raised in 1980 when Bess *et al.* reviewed 1153 patients and showed the coexistence or history of pancreatitis in only 1.5% of patients and suggested that the association may be casual rather than causal.[6] One possible reason for this turn could be the changing profile of PHPT in the developed countries, where symptomatic disease remains uncommon and pancreatic disease with PHPT extremely rare. Much later publications dealing with parathyroid disease are hesitant to attribute a direct causal linkage between the two and underplay the association. After the 1980s various studies from developed countries have shown the association of pancreatitis with PHPT to range from 3.2 to 5.6%.[7–9] Data from other developing countries show this association in approximately 2.5% of patients.[10,11]

One centre from the northern India has reported that in 6.8% of patients with PHPT, the disease was initially suspected because of unexplained pancreatic disease.[12] As pancreatic disease remains an important initial clinical presentation in the present setting, we attempt to characterize it in patients with PHPT in terms of their clinical presentation, biochemistry and imaging parameters.

PATIENTS AND METHODS

This study is a retrospective review of the medical records of 13 patients of a total of 101 PHPT patients who presented with pancreatic disease at Christian Medical College, Vellore between 1 May 2000 and 30 May 2005. The medical records were reviewed for patient characteristics and clinical details. Biochemical records of all 101 patients with PHPT were retrieved from the computerized hospital information processing system. The patients were divided into group 1 having PHPT with pancreatic disease and group 2 having PHPT without pancreatic disease.

J. J. Jacob MD; **M. John** MD, DM; **N. Thomas** MD, MNAMS, FRACP (Endo); **A. Chacko** MD, DM; **R. Cherian** MD; **B. Selvan** MS; **A. Nair** MS; **M. S. Seshadri** MD, PhD (Endo), FRCP.

Correspondence: Nihal Thomas, Department of Endocrinology, Christian Medical College, Vellore, TN, India 632004.
Email: nihal_thomas@yahoo.com

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The diagnosis of pancreatitis was confirmed by detection of an increased serum amylase (>3 times the normal) and/or increased lipase levels in the presence of upper abdominal pain. The diagnosis was confirmed by the presence of abnormalities on pancreatic imaging. Other aetiologies of pancreatic disease including gall bladder disease, microliths in bile, hypertriglyceridaemia, history of alcohol intake, medications and abdominal trauma were sought.

The biochemical diagnosis of PHPT was made when persistent increased calcium levels above the upper limit of normal was associated with an increased circulating immune reactive intact parathyroid hormone levels. The calcium values were corrected for the serum albumin values and the results were expressed as corrected calcium levels.

Detailed radiological reports were obtained from the picture archiving and communicating system (General Electric–Picture Archiving and Communicating System) and reviewed with a radiologist.

Data were analysed using the Statistical Program for Social Sciences (SPSS version 11.0 for Windows; SPSS, Chicago, IL, USA). Descriptive statistics were used in most of the reviews as the patient number was small.

RESULTS

Demography

Thirteen patients were identified from among a cohort of 101 (~13%) patients with confirmed PHPT who had clinical or anatomical evidence of pancreatic disease over a period of 5 years in our hospital. During the same period, there were 1284 admissions for pancreatic disease out of 302 883 inpatient admissions. In 12 patients (~12%) pancreatic disease was the presenting symptom and the initial clinical indication to make an assessment for parathyroid disease. One patient had pancreatic involvement in addition to severe bone disease as the presenting symptom. The patients ranged from 22 to 52 years in age with a median age of 37 years. The median age of patients in group 2 was 43 years. There were 9 (69%) men and 4 (31%) women among patients in group 1. Among patients in group 2 there were 38 (43%) men and 50 (57%) women.

Clinical manifestation of pancreatic disease

The common presentation of pancreatic disease was either recurrent episodes of upper abdominal pain seen in 6 (46%) of the 13 patients or a single episode of acute pancreatitis seen in another 6 (46%) of these patients. One of the patients mentioned had an episode of life-threatening acute pancreatitis requiring surgical intervention. One patient (8%) presented with a painless chronic pancreatitis characterized by malabsorption and secondary diabetes. The duration of symptoms before the diagnosis of PHPT was made ranged from a few days to 22 years. The median period before the diagnosis of PHPT was entertained was 6 months. Six (46%) of the patients had more than five episodes of pain, requiring an average of four hospital admissions for treatment of pain before surgery could be undertaken for the parathyroid adenoma. Significant weight loss was seen in five (38%) of the patients. However, malabsorption was documented in only one patient (8%). Other causes of pancreatitis were sought in all patients. Nine patients (69%) had a normal gall bladder on ultrasound imaging, whereas three (23%) had echogenic sludge in the gall bladder and in one (8%) patient the gall bladder could not be observed because of prior cholecystectomy. One patient (8%) had history of chronic alcohol dependence.

Other manifestations of hyperparathyroidism

Symptomatic nephrolithiasis was seen in 6 (46%) patients in group 1. Of the six patients with renal stones, one (8%) patient had bilateral stone disease, one (8%) had unilateral stone disease and four (30.8%) had nephrocalcinosis. Two patients (15%) had a history of bone pains whereas three (23.1%) had proximal muscle weakness. Two (15%) patients had a history of pathological fractures and one (8%) patient had a palpable mass in the neck. Among patients in group 2, bone disease was present in 60% of patients with 28% having severe bone pains, 31% had proximal muscle weakness, 37% had pathological fractures, 26% had radiological osteitis fibrosa cystica (OFC), 13% had palpable OFC and 3% had spinal deformities at the time of presentation. Symptomatic renal stones were seen in 36% patients, including 16% with the presence of renal parenchymal calcification. A palpable neck nodule was felt in 11% of patients. The median duration of symptoms in group 2 patients before the diagnosis of PHPT was 24 months.

Biochemical profile

Details of the biochemical profiles of groups 1 and 2 are shown in Table 1.

Imaging characteristics of the pancreas

The pancreatic anatomy of group 1 patients was characterized with either ultrasound or computed tomography (Fig. 1). The details are provided in Table 2.

Localization studies and surgical outcomes

Of the eight patients who underwent ultrasound of the neck, four (50%) had detectable lesions on the scan. A ^{99}technetium sestamibi scan was carried out on all patients. Eleven of them had unequivocal uptake that was suggestive of a single adenoma and two had a doubtful uptake. Surgical details are shown in Table 2. No postoperative complications were observed except for transient hypocalcaemia in two of the patients operated on.

DISCUSSION

The association of primary hyperthyroidism with pancreatic disease has been controversial because of the rarity of the association in contemporary published work in developed countries.

Table 1. Details of biochemical values in patients of group 1 and group 2

Biochemistry	Group 1 (n = 13)	Group 2 (n = 88)	P-value
Mean ± SD corrected calcium values (mmol/L)	3.32 ± 0.52	2.97 ± 0.25	0.006
Mean ± SD fasting inorganic phosphate values (mmol/L)	0.73 ± 0.18	0.74 ± 0.18	0.56
Mean ± SD SAP values (IU)	320 ± 296	426 ± 549	0.16
Mean ± SD iPTHvalues (ng/L)	345 ± 194	623 ± 714	0.13

iPTH, intact parathyroid hormone levels; SAP, serum alkaline phosphate.

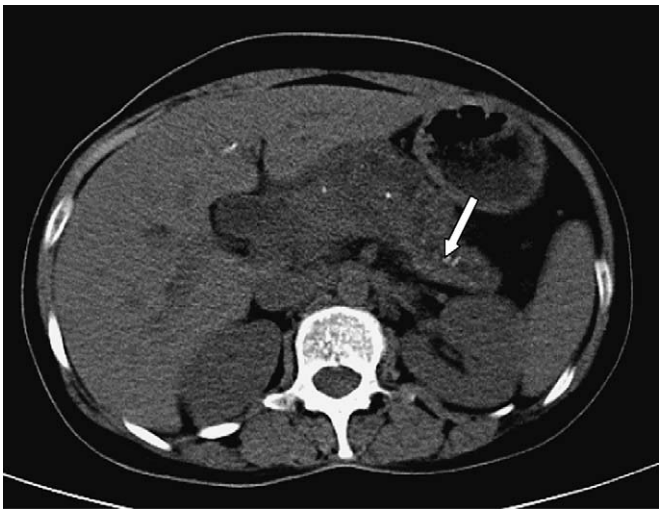

Fig. 1. Computed tomography scan of the abdomen showing bulky pancreas with dilated main pancreatic duct, intraparenchymal calcification and intraductal calculi (arrow).

The first critical report was published by Bess *et al.* from Mayo Clinic in 1980.[6] Of 1153 patients with surgically confirmed PHPT operated on at their centre between 1950 and 1975, only 17 (1.5%) had coexisting or prior pancreatitis. This frequency approximated the reported incidence of pancreatitis among patients admitted to the hospital without PHPT. Other factors of possible aetiological significance in pancreatitis, such as gallstones or alcohol abuse, were present in 11 of the 17 patients. The rarity of the association in their series led them to conclude that there is no direct causal correlation between the two diseases. A later publication from the same centre established that the majority of patients undergoing surgery for PHPT at that centre were asymptomatic with mild hypercalcaemia.[13] Data from hospitals with large volume of patients with symptomatic parathyroid disease have shown an association, which cannot be ignored. Shepherd was the first to review this from Australia where the association of pancreatic disease was present in 7 (5.1%) patients among the 137 who were treated for hyperparathyroidism.[7] Subsequent publications from Germany and France showed 5.6 and 3.2% of patients treated for PHPT had pancreatic disease.[8,9] Descriptive studies from Jordan, Saudi Arabia and North India, all describe patients with pancreatic disease among proven PHPT.[10–12]

The present series shows that 12% of patients with PHPT had pancreatic disease. During the period of 5 years, there were 1284 patients admitted with pancreatic disease and 101 patients admitted with PHPT to our hospital, accounting for 0.42 and 0.03%, respectively, of the total hospital inpatient admissions of 302 883. Among them, 13 patients had both pancreatic disease and PHPT accounting for 1% of all admissions for pancreatic disease. Of the 13 patients, 5 had additional possible causes for pancreatic disease. Three had gall bladder sludge, one had a history of gallstones requiring surgery and one patient had a history of alcoholism. Even if these patients are to be excluded, there are 8 patients (8%) among the 101 who had no other documented cause for pancreatic disease other than the hypercalcaemia associated with PHPT. The calculated relative risk of having pancreatic disease in patients admitted with PHPT was 28 compared with inpatients without PHPT. Similarly, the data suggest that patients admitted with pancreatic disease have 33-fold increased chances of having PHPT compared with patients admitted with non-pancreatic disease. Therefore, we suggest that there is a significant association between the two disorders.

Characterization of the pancreatic disease in hyperparathyroidism

In the present series, PHPT presents as pancreatic disease in much younger patients compared with the median age of presentation in isolated PHPT. The sex distribution also shows a male preponderance with the male : female ratio being almost 2:1. This is in contrast to the female preponderance we see in PHPT without associated pancreatic disease. In the largest series of patients with PHPT and pancreatic disease, over 40 patients were identified among 1224 patients operated for PHPT over a period of 30 years.[9] Among them, the mean age in patients with pancreatitis and PHPT was 52.5 compared to 55.5 in patients with PHPT without pancreatic disease. The male : female ratios were 1.1:1 and 0.34: 1, respectively.

Table 2. Details of patient and imaging characteristics and operative findings in group 1

Patient characteristics			Imaging characteristics					Operative findings	
n	Age	Sex	Size	Intra-parenchymal calcification	Ductal calculi	Main pancreatic duct	Peri-pancreatic collection	Operated	Localization of the adenoma
1	52	F	Normal	No	No	Normal	No	Yes	Right lower
2	40	M	Enlarged	No	No	Dilated	No	Yes	Left lower
3	45	M	Enlarged	Yes	No	Normal	Single	Yes	Left lower
4	38	F	Enlarged	Yes	Yes	Not known	Single	Yes	Right lower
5	34	M	Normal	No	No	Normal	No	Yes	Left lower
6	30	M	Enlarged	No	No	Dilated	No	Yes	Ectopic
7	22	M	Normal	No	No	Normal	No	Yes	Left lower
8	38	F	Enlarged	Yes	Yes	Dilated	Single	No	NA
9	35	M	Enlarged	Yes	Yes	Dilated	Single	Yes	Right lower
10	37	M	Enlarged	No	No	Normal	No	No	NA
11	45	F	Enlarged	Yes	Yes	Not known	No	Yes	Left lower
12	35	M	Enlarged	No	No	Normal	Single	Yes	Left lower
13	47	M	Enlarged	No	No	Normal	No	Yes	Left upper

F, female; M, male; NA, not applicable.

The commonest manifestation of pancreatic disease with PHPT is the history of recurrent upper abdominal pain (50%). In the majority, the pancreatic origin of the disease is clarified once serum amylase or serum lipase levels are obtained. The mean duration of symptoms before the patients were found to have PHPT ranged from 6 months to 22 years. The median time before a diagnosis could be established was 24 months. Patients had, on an average, four hospitalizations and over 10 episodes of pain before the underlying hypercalcaemia was identified. This delay in the diagnosis could have been avoided if calcium values were checked in all patients with unexplained pancreatic disease at the first instance.

In 1966, Pyrah *et al.* had attempted to summarize the circumstances under which pancreatic disease was found in association with PHPT.[14] Modifying this, we can classify presentation of pancreatic disease in PHPT into four important classes:

- PHPT presenting as acute pancreatitis
- PHPT presenting as acute recurrent pancreatitis with no evidence of chronic pancreatitis
- PHPT presenting as chronic pancreatitis with or without pancreatic calcification
- PHPT complicated by acute pancreatitis in the postoperative period

We reviewed the clinical presentation in 87 patients from five case series including 13 patients from the present series (Table 3). Class 1 presentation was the most common, occurring in over 44% of patients, underlining the need to check calcium values in all patients presenting with the first episode of pancreatitis. We did not have any documented reports of patients who developed acute pancreatitis in the postoperative period. In over one-third of the patients the disease was more insidious and presented with evidence of chronic pancreatitis. Parathyroid surgery at this point may not reverse the pancreatic pathology and long-term therapy for exocrine and endocrine pancreatic insufficiency may be required. However, it would be still be prudent to check serum calcium levels in these patients as early parathyroid surgery would prevent associated renal and bone disease.

Hypercalcaemia as the mediator of pancreatic injury in PHPT

In animal models acute pancreatitis has been induced, when a two-fold increase in serum ionized calcium was obtained by either bolus injections or by continuous infusion of calcium.[16] Pathological changes of early acute pancreatitis with hypercalcaemia has been observed in several animal species.[17,18] It was shown that hypercalcaemia induced a secretory block and accumulation of digestive zymogens within the pancreatic acinar cells.[19] In humans, development of acute pancreatitis has been linked to the use of therapeutic i.v. calcium administration. Among patients undergoing cardiac surgery, evidence of pancreatic injury was seen in 27% of patients. Although ischaemia secondary to hypoperfusion is considered to be the cause of this complication, the administration of large doses of calcium chloride was an independent predictor of pancreatic cellular injury.[20]

The molecular mechanism of hypercalcaemia-mediated pancreatic injury has still not been elucidated and remains a matter of conjecture. We know that the earliest abnormalities of acute pancreatitis arise within the acinar cells and that calcium is a vital intracellular second messenger in the acinar cell for initiating enzyme release through phosphorylation cascades. The cytoplasmic concentration of calcium is tightly regulated.[21] Sustained levels of acinar cytoplasmic calcium may cause damage to the acinar cells by the unopposed activation of zymogens, including trypsinogen.[20] Various factors, including alcohol abuse, ductal hypertension, ischaemia, hyperlipidaemia, viral infections and hypercalcaemia may trigger acute pancreatitis by increasing intracytoplasmic calcium levels. In the present series all patients had corrected serum calcium above the normal range (normal levels; 2.07–2.60 mmol/L). The mean calcium values were significantly higher among patients with PHPT and pancreatic disease compared with patients with PHPT without pancreatic involvement. This suggests that the mechanism of development of pancreatic disease in PHPT is correlated to the hypercalcaemia. These observations suggest that hypercalcaemia per se, in addition to being an independent risk for the precipitation of pancreatic cellular injury, could also augment pancreatic disease in patients with ongoing pancreatic injury because of other causes.

In the present series we have shown a higher association of PHPT and pancreatic disease than any previous series. We postulate two possible reasons for this. First, parathyroid disease in the present study is a largely symptomatic disease similar to the presentation of PHPT seen in the last century in the West. That could account for a higher percentage of patients having associated pancreatic disease.

Second, unusual pancreatic diseases like tropical chronic pancreatitis (TCP), a form of chronic calcific non-alcoholic pancreatitis are a common cause of chronic pancreatitis at our centre. The exact aetiopathogenetic mechanisms of TCP remain elusive, but it has been suggested that various factors like malnutrition, dietary toxins and familial and genetic factors contribute to the development of the disease.[22] We propose that the presence of hypercalcaemia correlated to PHPT among patients susceptible to TCP may cause an unmasking of preclinical and subclinical diseases. The presence of large intraductal calculi similar to that seen in TCP in 30% of patients in our series may point to that possibility. A combination could account for the frequency of the association.

Eleven of the 13 patients underwent parathyroid surgery. Most of the tumours (excluding one) were situated in the lower part of the neck of operated patients. Long-term follow up was available only in a limited number of patients. The natural history of chronic pancreatitis correlated to PHPT is still not clear as most patients had a limited follow up.

Table 3. Details of presentation of pancreatic disease in PHPT from four other case series in the published work

	Bess *et al.*[6] (n = 17)	Sitges-Serra *et al.*[15] (n = 10)	Shepherd *et al.*[7] (n = 7)	Carnaille *et al.*[9] (n = 40)	Present series (n = 13)	Total (n = 87)(%)
Class 1	8	6	4	18	3	39 (44.8%)
Class 2	—	1	2	8	3	14 (16.1%)
Class 3	7	3	—	14	7	31 (35.6%)
Class 4	2	—	1	—	—	3 (3.4%)

CONCLUSIONS

The present study suggests a causal association between the pancreatic disease and PHPT. The frequency of the disease in our setting probably correlates to the large number of symptomatic PHPT that we see in our country. We propose that other undefined factors that predispose our patients to tropical pancreatitis may also unmask subclinical/preclinical pancreatic disease early in the course of PHPT. The disease is more common in younger individuals with a male preponderance. The disease is correlated to higher calcium values in PHPT. The exact cellular mechanism by which hypercalcaemia causes pancreatic injury in PHPT remains to be elucidated. Until more information is available, it would be prudent to check serum calcium in all patients presenting with unexplained pancreatic disease.

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