

## GASTROENTEROLOGY

# Chronic pancreatitis in primary hyperparathyroidism: Comparison with alcoholic and idiopathic chronic pancreatitis

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## Key words

diabetes mellitus, pancreatitis, parathormone, parathyroidectomy, steatorrea.

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## Abstract

**Background:** Primary hyperparathyroidism is a rare cause of chronic pancreatitis and there is a paucity of data on this interesting association. There is also no data comparing the clinical profile of chronic pancreatitis secondary to primary hyperparathyroidism with that of alcohol related and idiopathic chronic pancreatitis.

**Methods:** The clinical and biochemical spectrum of chronic pancreatitis secondary to primary hyperparathyroidism was evaluated retrospectively and compared with nine age-matched patients with alcohol related and idiopathic chronic pancreatitis.

**Results:** Renal colic, nephrolithiasis, nephrocalcinosis, bone disease, palpable neck nodule, and psychiatric abnormality were significantly more common in chronic pancreatitis due to hyperparathyroidism in comparison to alcoholic and idiopathic groups. The corrected calcium ( $10.8 \pm 0.9$  vs  $9.3 \pm 0.6$  vs  $9.2 \pm 0.8$  mg/dL;  $P = 0.001$ ) and intact parathormone ( $425 \pm 130$  [SE] vs  $22.2 \pm 14.3$  [SE] vs  $30 \pm 27.3$  [SE] pg/mL;  $P = 0.009$ ) levels were significantly elevated, while levels of serum phosphate were significantly less ( $3.1 \pm 0.4$  vs  $3.9 \pm 0.5$  vs  $3.4 \pm 0.7$  mg/dL, respectively;  $P = 0.04$ ) in chronic pancreatitis due to hyperparathyroidism in comparison to the alcoholic and idiopathic groups. No significant difference was observed in the frequency of steatorrea, diabetes mellitus, pancreatic calcification, and pseudocyst between the three groups. Six out of nine patients underwent parathyroidectomy and none had recurrence of pancreatic pain over  $14.3 \pm 13.8$  months.

**Conclusions:** Chronic pancreatitis due to hyperparathyroidism has important characteristics in its biochemical and clinical manifestations. Parathyroidectomy relieves pancreatic pain in majority of patients.

## Introduction

Chronic pancreatitis (CP) is characterized by continuing inflammatory disease of the pancreas leading to irreversible morphologic changes which typically cause pain and/or permanent loss of function.<sup>1</sup> The common causes of CP include chronic alcohol abuse (CP-ALC), idiopathic pancreatitis (CP-ID), hyperparathyroidism, hereditary pancreatitis, tropical pancreatitis, autoimmune pancreatitis, and hypertriglyceridemia.<sup>1</sup> Primary hyperparathyroidism (PHPT) is a rare cause of both acute pancreatitis and CP with a reported prevalence of less than 0.1–4% of CP cases.<sup>1–3</sup> Although Bess *et al.*,<sup>4</sup> on the basis of their observation of similar incidences of pancreatitis in patients with hyperparathyroidism (17/1153; 1.5%) and general hospital patient population, have reported that there is no association between CP and hyperparathyroidism, many case reports<sup>5–18</sup> and case-series<sup>17–26</sup> have provided substantial

evidence to suggest an association between these two disorders; and hyperparathyroidism is now an accepted etiology of acute and recurrent acute pancreatitis and CP.<sup>1,20</sup>

The published experience of CP secondary to PHPT is limited to case reports, case series or parts of studies describing both acute pancreatitis and CP secondary to PHPT.<sup>5–26</sup> Moreover, the detailed recording of clinical and biochemical characteristics of patients with CP due to PHPT (CP-PHPT) are lacking in majority of these studies. Also, during our research we could not find published data comparing the clinical profile of CP-PHPT with other forms of chronic pancreatitis such as CP-ALC and CP-ID. In order to study the detailed profile of patients with CP-PHPT, the clinical and biochemical data of nine patients with CP secondary to PHPT seen at our center were retrospectively reviewed and compared with that of nine age-matched patients with CP-ALC and CP-ID seen during the same period.

## Methods

The hospital records of patients diagnosed with CP secondary to PHPT at a tertiary care center in North India between 2001 and 2005 were retrospectively reviewed. The diagnosis of CP was based on clinical, biochemical, and radiological parameters.<sup>1</sup> The diagnosis of PHPT was based on biochemical or surgical criteria.<sup>20,21</sup> Biochemical criteria meant patients displayed raised serum intact parathormone levels (normal, 7–53 pg/mL) with or without persistently raised corrected serum calcium levels (normal, 9–11 mg/dL), excluding other causes of hypercalcemia. The intact parathormone was measured by two-site chemiluminescent solid phase immunoassay (Imulid).<sup>27</sup> Localization of hyper-functioning parathyroid was done using ultrasound neck, computed tomography of neck, and sestamibi scan.<sup>28,29</sup> Surgical criteria meant histological proof of parathyroid adenoma following parathyroidectomy. Patients with concomitant gallstones, history of alcohol consumption, hypertriglyceridemia, and hereditary pancreatitis were excluded.

The diagnosis of CP-ALC was considered in patients who had consumed more than 50 g/day of alcohol for at least five years with features of CP.<sup>30–32</sup> The diagnosis of CP-ID was considered in patients without hereditary pancreatitis (as determined by family history), those without pre-existing disorders likely to cause CP (hypertriglyceridemia, primary hyperparathyroidism, abdominal trauma, and pancreatic duct stenosis secondary to operation), and patients in whom excessive alcohol consumption could be absolutely ruled out.<sup>33</sup>

To describe the characteristic and differentiating clinical and biochemical features, nine patients with CP-PHPT were compared with nine randomly selected age-matched patients with CP-ALC and CP-ID who were seen in our clinic during the same period, with respect to clinical manifestations and biochemical profile including serum amylase, fasting and post prandial sugar, serum calcium, serum phosphate, serum alkaline phosphatase (SAP), serum triglyceride, and serum intact parathormone (iPTH). Also, nine patients with CP-PHPT were compared with 44 PHPT patients without CP seen during the same period, for clinical and biochemical parameters.

All patients with CP were analyzed for presence or absence of abdominal pain, number of attacks of acute pancreatitis, mode of presentation, alcohol consumption, and family history of pancreatitis. Other factors included renal colic, bone pain, fracture or deformity, neck nodule, and psychiatric manifestation. The complications of pancreatitis, such as exocrine insufficiency, diabetes mellitus, calcification, and pseudocyst were also noted. Bone disease was defined as presence of fracture, bone pain, or decreased bone mineral density on dual energy X-ray absorptiometry (DEXA). DEXA was done only in patients with CP-PHPT and not in the other two CP groups.

## Statistical analysis

The Statistical Program for the Social Sciences (Release 10.0.1; SPSS Inc, Chicago, IL) was used for data analysis. Data are expressed as mean  $\pm$  SD unless specified. In addition to descriptive statistics, the  $\chi^2$ -squared test was used for comparison between categorical variables and the Student's *t*-test was used in comparing continuous variables. ANOVA followed by a post hoc

**Table 1** Comparison of clinical variables across the three chronic pancreatitis groups secondary to hyperparathyroidism, alcohol, and idiopathic variety

	CP-PHPT ( <i>n</i> = 9)	CP-ALC ( <i>n</i> = 9)	CP-ID ( <i>n</i> = 9)
Age in years (mean $\pm$ SD)	42.5 $\pm$ 10.6	41.8 $\pm$ 8.4	35.6 $\pm$ 13.3
Gender (no. of males/females)	4/5*	9/0	3/6
Renal colic	9 (100)**	0	0
Nephrolithiasis	9 (100)**	0	0
Nephrocalcinosis	4 (44.4)***	0	0
Bone disease	4 (44.4)***	0	0
Neck nodule <sup>†</sup>	4 (44.4)***	0	0
Psychiatric abnormalities	6 (66.6)****	0	0
Steatorrea	2 (22.2)	0	0
Diabetes mellitus	4 (44.4)	1 (11.1)	1 (11.1)
Pancreatic calcification	5 (55.5)	4 (44.4)	6 (66.6)
Pseudocysts	2 (22.2)	4 (44.4)	1 (11.1)

\**P* = 0.005; \*\**P* = 0.000; \*\*\**P* = 0.018; \*\*\*\**P* = 0.001.

<sup>†</sup>Palpable parathyroid gland.

Data are numbers (percentage) wherever not specified.  $\chi^2$ -squared test was used for comparison between categorical variables.

CP-PHPT, chronic pancreatitis caused by primary hyperparathyroidism; CP-ALC, chronic pancreatitis caused by alcohol abuse; CP-ID, idiopathic pancreatitis.

Scheffé test was used to compare the continuous variables across the three CP groups. All *t*-values were calculated as two-tailed and *P* < 0.05 was considered significant.

## Results

Fifty-nine PHPT patients were seen at our institute; 11 (18.6%) of these had CP. Two patients were excluded, as there was a history of significant alcohol intake. Hence, nine (15.2%) patients were considered as having CP-PHPT; and these nine patients were compared with nine randomly selected age-matched patients with CP-ALC and CP-ID seen during the same period (Tables 1,2). Also nine CP-PHPT patients were compared with 44 PHPT patients for clinical and biochemical variables (Table 3).

## Gender

There were four males and five females in the CP-PHPT group, whereas there were nine males in the CP-ALC group and three males and six females in the CP-ID group. Hence, the male to female ratio was significantly more in the CP-ALC group than in the CP-PHPT and CP-ID groups (*P* = 0.005) as shown in Table 1. The male to female ratio was not different in patients with CP-PHPT and PHPT without CP (*P* = 0.19, Table 3).

## Clinical features

The mean duration of illness was not significantly different among the CP-PHPT, CP-ALC and CP-ID groups (73  $\pm$  69.5, 39  $\pm$  35.4, and 73  $\pm$  69.5 months, respectively; *P* = 0.16). Abdominal pain was present in all CP-PHPT patients, as with the other two CP groups and there was no statistically significant difference. As all

**Table 2** Comparison of biochemical parameters across the three groups of chronic pancreatitis secondary to hyperparathyroidism, alcohol and idiopathic variety

	CP-PHPT (n = 9)	CP-ALC (n = 9)	CP-ID (n = 9)
S. Calcium (mg/dL)	10.8 ± 0.9*	9.3 ± 0.6	9.2 ± 0.8
S. Phosphate (mg/dL)	3.1 ± 0.4**	3.9 ± 0.5	3.4 ± 0.7
S iPTH (pg/mL) <sup>†</sup>	425 ± 130***	22.2 ± 14.3	30.0 ± 27.3
S ALP (kAU) <sup>†</sup>	22.0 ± 6.9	8.4 ± 2.2	12.6 ± 11.4
S. Amylase (IU)	293 ± 98	246.6 ± 208	228.2 ± 142.2
Fasting blood sugar (mg/dL)	95.5 ± 26.7	98.4 ± 19.4	99.11 ± 27.6
2 h PP blood sugar (mg/dL)	130.3 ± 41.8	141.8 ± 30.9	173.6 ± 41.8
S. triglycerides (mg/dL)	135 ± 53	112 ± 33.6	142.7 ± 63.4

\* $P = 0.001$ ; \*\* $P = 0.04$ ; \*\*\* $P = 0.009$ .

<sup>†</sup>Mean ± standard error of mean.

Data are mean ± SD unless otherwise specified.  $P$ -values denote comparison across the three groups by ANOVA.

CP-ALC, chronic pancreatitis caused by alcohol abuse; CP-ID, idiopathic pancreatitis; CP-PHPT, chronic pancreatitis caused by primary hyperparathyroidism; iPTH, intact parathormone; PP, post prandial.

**Table 3** Comparison of clinical and laboratory parameters in PHPT patients without CP and CP-PHPT patients

	CP-PHPT (n = 9)	PHPT (n = 44)	$P$ -value
Age in years <sup>†</sup>	42.5 ± 10.6	38.4 ± 11.8	0.31
Gender (male/female)	4/5	9/35	0.19
Renal colic	9 (100)	18 (40)	<b>0.001</b>
Nephrolithiasis	9 (100)	22 (50)	<b>0.007</b>
Nephrocalcinosis	4 (44.4)	10 (22.7)	0.22
Bone disease	4 (44.4)	36 (81.8)	<b>0.03</b>
Psychiatric abnormality	6 (66.6)	14 (32.6)	0.07
Palpable neck nodule	4 (44.4)	12 (27.3)	0.42
Steatorrea	2 (22)	0 (0)	<b>0.02</b>
Diabetes mellitus	4 (44.4)	1 (2.3)	<b>0.002</b>
S. calcium (mg/dL) <sup>†</sup>	10.8 ± 0.9	10.9 ± 1.2	0.76
S. phosphate (mg/dL) <sup>†</sup>	3.1 ± 0.4	3.0 ± 0.6	0.51
S. iPTH (pg/mL) <sup>†</sup>	425 ± 130	1145 ± 199	<b>0.004</b>
SAP (mg/dL) <sup>†</sup>	22.0 ± 6.9	42.3 ± 9.2	0.09

<sup>†</sup>Data are mean ± SD; otherwise data are expressed as numbers (percentages).

<sup>†</sup>Mean ± SEM.

$P$ -value by  $\chi^2$ -squared test for categorical variables and Student's  $t$ -test for continuous variables.

CP-PHPT, chronic pancreatitis caused by primary hyperparathyroidism; iPTH, intact parathormone levels; PHPT, primary hyperparathyroidism; SAP, serum alkaline phosphatase.

the nine patients with CP-PHPT had associated renal calculi, pain located in the upper abdomen with or without radiation to the back was considered to be due to pancreatitis, whereas pain located in lumbar region radiating to the groin with or without associated burning micturition was considered to be due to renal calculi. In patients of CP due to PHPT, pancreatic pain was the presenting manifestation in six patients, renal colic in two patients and bone disease in one patient, whereas in the other two groups of CP, abdominal pain was the presenting manifestation in all patients. There were two patients who had one episode of pancreatitis, two patients had two episodes, and three patients had more than two

episodes, but exact number was unknown and one patient each had three and four episodes of pancreatitis in the CP-PHPT group. Of the nine patients with CP, pancreatic calcification was present in five (55.5%) patients. As shown in Table 1, renal colic, nephrolithiasis, and nephrocalcinosis were significantly more common in the CP-PHPT group in comparison to the CP-ALC and CP-ID groups ( $P$ -values, 0.000, 0.000, and 0.018, respectively). Similarly, bone disease, palpable neck nodule, and psychiatric abnormalities were statistically more common in the CP-PHPT group than in the CP-ALC and CP-ID groups ( $P$ -values, 0.018, 0.018 and 0.001, respectively). Bone disease included bone fracture in one, bone pain in one and osteoporosis in two patients. Psychiatric abnormalities included irritability, depression, emotional lability, and psychosis.

The complications of CP such as steatorrea, diabetes mellitus, pancreatic calcification, and pancreatic pseudocyst were not statistically different across the three CP groups as shown in Table 1.

When patients of CP-PHPT were compared with PHPT patients without CP, renal colic, nephrolithiasis, steatorrea, and diabetes mellitus were significantly more common in the CP-PHPT group ( $P$ -values, 0.001, 0.007, 0.02 and 0.002, respectively), whereas bone disease was more common in patients with PHPT without CP ( $P$ -value, 0.03) as shown in Table 3.

### Biochemical parameters

The comparison of biochemical parameters between the three CP groups is presented in Table 2. The mean corrected calcium level was significantly higher in the CP-PHPT group than in the CP-ALC and CP-ID groups (10.8 ± 0.9 vs 9.3 ± 0.6 vs 9.2 ± 0.8 mg/dL, respectively;  $P = 0.001$ ). The mean serum phosphate level was significantly lower in the CP-PHPT group than in the CP-ALC and CP-ID groups (3.1 ± 0.4 vs 3.9 ± 0.5 vs 3.4 ± 0.7 mg/dL, respectively;  $P = 0.04$ ). The mean iPTH level was significantly higher in the CP-PHPT group than in the CP-ALC and CP-ID groups (425 ± 130 [SE] vs 22.2 ± 14.3 [SE] vs 30 ± 27.3 [SE] pg/mL, respectively;  $P = 0.009$ ). Other biochemical parameters such as serum amylase, serum alkaline phosphatase (ALP), blood sugar, and triglyceride levels were not different across the three CP groups.

Serum amylase more than three times the upper limit of normal was detected in one CP-ALC patient and this patient had pseudocyst with pancreatic ascites. Serum amylase was not raised more than three times the upper limit of normal in any of the patients in the other two groups. The range of amylase level was 160–400 IU in the CP-PHPT group, 160–800 IU in the CP-ALC group, and 160–400 IU in the CP-ID group.

When PHPT patients without CP were compared with CP-PHPT patients, the serum iPTH level was significantly more in the PHPT without CP group ( $1145 \pm 199$  [SE] vs  $425 \pm 130$  [SE] pg/mL, respectively;  $P = 0.004$ ). Other biochemical parameters were not statistically different between the two groups (Table 3).

### Effect of parathyroidectomy on clinical manifestations

Six of the nine CP-PHPT patients underwent parathyroidectomy. One patient died before surgery due to end stage renal disease. Two patients did not undergo surgery and were subsequently lost to follow up; these two patients suffered from steatorrhea and diabetes mellitus. All six patients who underwent parathyroid surgery had an adenoma involving a single gland. They were followed up for  $14.3 \pm 13.8$  months (6–36 months) and none had recurrence of CP pain or episodes of acute CP following parathyroidectomy. There were no further episodes of renal colic, except in two CP-PHPT patients following parathyroidectomy, who required lithotripsy for renal stones.

### Discussion

This study is a retrospectively built detailed profiles of nine CP-PHPT patients and compared profiles with those of nine randomly selected age-matched patients with CP-ALC and CP-ID seen during the same period. The small sample size in the current study limits any meaningful comparisons made between the three groups. Despite this limitation, detailed profiles of incidences of CP-PHPT, a rare disorder and previously only described in case reports and small case series, were established.

In various studies, the incidence of CP among patients with PHPT has been reported to be between 0.1 and 3.3%.<sup>4,12,19,21</sup> In the present study, 15.2% of PHPT patients had CP. The incidence of CP was higher in the present series, probably because of the high index of suspicion for hyperparathyroidism in cases of CP, or because of differences in geographic distribution.

In the present study, there were five females and four males in the CP-PHPT group. This is at variance with some CP-PHPT studies where there were more males (four out of six,<sup>19</sup> two out of three,<sup>20</sup> and 10 out of 15<sup>23</sup>). In one reported study, all three CP-PHPT patients were females.<sup>24</sup> There are single case reports of males<sup>6–8,10,18</sup> and females<sup>5,9,1,12,16,24</sup> affected by the disease. There were equal number of males and females in two reported studies.<sup>14,26</sup> In some studies, information on the gender ratio is lacking.<sup>4,21</sup>

There was a significant gender difference among the CP-PHPT, CP-ALC and CP-ID groups, because all patients with CP-ALC were males compared with the CP-ID and CP-PHPT groups. This is similar to other reports, as most CP-ALC patients were males.<sup>31,32</sup> When we compared our CP-PHPT and PHPT without CP patients, there were 35 females and nine males in the PHPT without CP group. This is similar to other studies, where the

number of female patients with PHPT was higher than male patients.<sup>14,20,21</sup>

Similar to the present study, where all CP-PHPT patients had pancreatic pain, other case reports and case series have also described the presence of abdominal pain as the predominant clinical manifestation.<sup>5,6,8–10,14,17,18,20,22,23,26</sup> In a study on six patients with CP-PHPT, acute attacks of pancreatitis were the presenting manifestation in three patients, diabetes mellitus in one patient and incidental diagnosis in two patients.<sup>19</sup> In the current study, all the nine patients had a prior history of one or more episodes of acute pancreatitis prior to presenting at our center. In other studies, recurrent attacks were seen in 3/6<sup>19</sup> and 7/15<sup>23</sup> patients, whereas a single episode of pancreatitis was seen in 3/6<sup>19</sup> and 5/15<sup>23</sup> patients; there was absence of pain in 3/15 patients although pancreatic calcification was evident.<sup>23</sup>

Renal colic, nephrolithiasis, and nephrocalcinosis were seen in nine (100%), nine (100%), and four (44.4%) patients, respectively, in the CP-PHPT group (Table 1). The exact incidence of nephrolithiasis and nephrocalcinosis in patients with CP-PHPT has not been previously reported. In two case-series on CP-PHPT, nephrolithiasis and nephrocalcinosis were seen in one patient each out of three cases.<sup>20,24</sup> Some of the case reports also mention the presence of nephrolithiasis and nephrocalcinosis in CP-PHPT.<sup>7,8,13,16</sup> Renal colic, nephrolithiasis, and nephrocalcinosis were not seen in any patients with CP-ALC and CP-ID, as these are manifestations of PHPT. Renal colic and nephrolithiasis was significantly more common in CP-PHPT patients (100% each) in comparison to PHPT without CP, where renal colic was seen in 40% of patients and nephrolithiasis in 50% of patients. The significance of this difference is not clear.

Bone disease was seen in four (44.4%) CP-PHPT patients in the form of bone pain, osteoporosis, and fracture. In two case series, one out of three CP-PHPT patients had bone disease.<sup>20,24</sup> While bone disease has been reported in various case reports in the form of osteitis fibrosa cystica,<sup>6,10</sup> bowed thighs,<sup>5</sup> and osteoporosis,<sup>11</sup> other studies have not reported bone disease in CP-PHPT patients.<sup>14,23</sup> Deformity and osteitis fibrosa cystica were not seen in any of our patients. Frank bone disease, in the form of fracture, pain, or deformity was not seen in any patient in the CP-ALC and CP-ID groups. However, bone mineral density testing using DEXA was not done for CP-ALC and CP-ID patients. Osteopenia and osteomalacia have been reported in patients of CP-ALC and CP-ID with severe exocrine insufficiency.<sup>34–36</sup> In patients with PHPT without CP, bone disease was seen in significantly more cases (81%) when compared to PHPT group (44%). Probably patients with CP have abdominal pain and hence seek medical evaluation early, during which parathyroid adenoma is detected and excised. This prevents the progression of the disease to the bones.

The neck nodule which represents the palpable parathyroid gland was noted in 4/9 (44.4%) of the patients; this has been reported earlier in only one case-report<sup>11</sup> and has not been reported in other studies on CP-PHPT.<sup>5–10,12–26</sup> Since the neck nodule was not palpable in any of the patients in the other two CP groups, it should be looked for in patients with CP as its presence may suggest PHPT as the etiology for CP.

In the current study, psychiatric manifestations in the form of irritability, depression, emotional lability, and psychosis were seen in 6/9 (66.6%) of the CP-PHPT patients. In contrast to this observation, an earlier study noted depression in one of three patients.<sup>24</sup>

Other studies on CP-PHPT have not reported psychiatric manifestations.<sup>5–26</sup> Since none of the other two CP groups had psychiatric manifestations and psychiatric manifestation is a feature of PHPT, any CP patient with irritability, emotional lability, depression, or psychosis should be examined for PHPT.

We observed diabetes mellitus in 4/9 (44%) of the patients and this observation is in accordance with the observations of Bauer *et al.*<sup>19</sup> who observed diabetes in 3/6 (50%) of patients; however it is higher than the 3/15 (20%) patients described by Carnaille *et al.*<sup>21</sup> Exocrine insufficiency as evident by clinical steatorrea was observed in 2/9 (22%) of patients. Earlier studies on CP-PHPT have reported exocrine insufficiency in 4/6 (66.6%),<sup>19</sup> 1/3 (33.3%),<sup>20,24</sup> and 6/15 (40%)<sup>23</sup> of patients. Various other case reports have also reported exocrine insufficiency.<sup>8,10–12,22,24,26</sup> Hence, exocrine and endocrine insufficiency is seen in CP-PHPT. Also, the endocrine and exocrine insufficiency were equally common in the three CP groups in the present study, indicating that CP-PHPT can also progress to later stages of CP (Table 1). Exocrine insufficiency and diabetes mellitus were significantly more common in CP-PHPT patients in comparison to those with PHPT without CP, indicating that CP should be thought of in patients of PHPT with pancreatic pain, steatorrea, and diabetes mellitus.

Corrected serum calcium and iPTH levels were significantly higher in the CP-PHPT group compared with the CP-ALC and CP-ID groups. This is because parathyroid adenoma secretes PTH, leading to increased calcium levels. Serum phosphate was significantly lower in the CP-PHPT group in comparison to the CP-ALC and CP-ID groups. This is probably due to the action of PTH which leads to increased renal excretion of phosphorus.<sup>37</sup> Also, the serum iPTH level was significantly higher in PHPT patients without CP in comparison to CP-PHPT patients. This is probably due to more the presence of advanced disease in patients without pancreatitis. CP-derived pain could have caused patients to seek medical advice and treatment earlier than patients with PHPT without CP where the disease was more severe. There was no difference in the rest of the biochemical profile in CP-PHPT patients and PHPT without CP patients.

In the present study, normal corrected calcium levels (9–11 mg/dL) were seen in 6/9 (66%) CP-PHPT patients. However, most of these patients had one or more of the following clinical features: renal colic, bone disease, nephrolithiasis, nephrocalcinosis, or psychiatric disorders. Even with normal corrected calcium levels, serum parathormone levels were raised in all patients. The entity of normocalcemic hyperparathyroidism has not been discussed in previous reported CP-PHPT cases. Although 25-hydroxy vitamin D3 was not measured in the patients in the current study, normocalcemic PHPT has been reported in 15–50% of Indian PHPT patients, probably because of underlying vitamin D deficiency.<sup>38,39</sup>

In the present study, pancreatic calcification was seen in 50% of CP-PHPT patients (Table 1) and this observation is similar to that of Herskovic *et al.*,<sup>23</sup> who reported calcification in 6/15 (40%) CP-PHPT patients. In contrast, some studies have reported a frequency of pancreatic calcification as high as 66–100% in CP-PHPT patients.<sup>19,20</sup> Calcification was seen in 4/9 (44%) of the CP-ALC and 6/9 (66%) of the CP-ID patients and this frequency was not significantly different from that observed in CP-PHPT patients. Also, the presence of pancreatic pseudocysts was not different among the CP-PHPT, CP-ALC and CP-ID groups, indicating that complications of CP-PHPT may not be different from

other two CP groups. The pseudocysts in both patients were seen before the diagnosis of PHPT and were located in the lesser sac. One patient underwent cystogastrostomy prior to diagnosis of PHPT and in the other patient, the pseudocyst resolved spontaneously over two months. In different reports, pseudocysts in CP-PHPT patients have resolved spontaneously or have been treated with surgery.<sup>14,26</sup>

Six patients underwent surgery and in all of them the adenoma involved a single gland in the neck. Like the present study, parathyroid adenoma was seen histologically in most of the other studies on CP-PHPT.<sup>5,7–9,11,12,14,16–18,24,26</sup> Hyperplasia of the parathyroid glands<sup>6,14</sup> and adenoma at an ectopic site<sup>17</sup> have been reported as a cause in other studies, whereas the details of histology are lacking in some of the studies.<sup>20,21</sup> Following resection of the parathyroid adenoma, it is interesting to note that none of the patients had recurrences of pancreatic pain, despite established CP, over a follow up of 6–36 months. These results are similar to other studies in which patients were relieved of pain after parathyroidectomy.<sup>9,14,24,26</sup> However, in some other studies not all patients were relieved of pain following parathyroidectomy.<sup>19–21</sup> In a study of seven patients who underwent parathyroidectomy, five patients were asymptomatic, one patient had a recurrence of pain two years after parathyroidectomy, and one patient went on to develop exocrine insufficiency.<sup>22</sup> In another study, 9/13 patients who underwent parathyroidectomy experienced no pain after a follow-up period of 15 months to 12 years. One patient continued to have abdominal pain after parathyroidectomy, although pain was less frequent and severe; however, information on three patients in the study was missing.<sup>23</sup> In another report, pain persisted after parathyroidectomy and required pancreatic surgery because of the presence of multiple stones in pancreatic duct.<sup>17</sup> The mechanism of pain resolution after parathyroidectomy is speculative. The factors responsible for pain in CP are not completely understood and perhaps multifactorial, including inflammation, duct obstruction, high pancreatic tissue pressure (compartment syndrome), fibrotic encasement of sensory nerves, and a neuropathy characterized by both increased numbers and sizes of intrapancreatic sensory nerves, and by inflammatory injury to the nerve sheaths allowing exposure of the neural elements to toxic substances.<sup>40,41</sup> In patients with PHPT, increased serum parathormone levels and consequently elevated serum calcium levels may increase the pancreatic inflammation and thus pain. Following parathyroidectomy, normalized serum parathormone levels and calcium levels may lead to decreased pancreatic inflammation and this may be one of the factors leading to improvement in pain following parathyroidectomy. It has been suggested that although changes caused by acute pancreatitis resolve after parathyroidectomy, patients with CP may go on to develop diabetes mellitus, pancreatic duct dilation, and splenic vein thrombosis.<sup>21</sup>

In conclusion, renal colic, nephrolithiasis, nephrocalcinosis, bone disease, psychiatric manifestations, and neck nodules are important clinical parameters that can help in differentiating CP-PHPT from other types of CP. Biochemical markers that favor CP-PHPT include high corrected calcium, low phosphate, and high intact parathormone levels. In suspected patients, even if corrected calcium is normal, serum iPTH should be checked to rule out hyperparathyroidism. Parathyroidectomy reduces the pain of CP and renal colic. However, further studies are required to assess the evolution of exocrine and endocrine functions, structural

changes of the pancreas, nephrolithiasis, and nephrocalcinosis following parathyroidectomy.

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