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Systematic Review

Relationship between Hypercalcemia and Pancreatitis: A Systematic Review Article

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Abstract

Introduction: Among the many causes of pancreatitis, primary hyperparathyroidism (PHPT) is rarely associated with pancreatitis. However, the causal relationship between the two is still controversial. Our aim was to investigate and describe the nature of pancreatic disease in PHPT.

Methods: In the present systematic review, all qualitative articles related to the objectives of the study, published from 2008 to January 2024, were reviewed. Search in Magiran database, IranDoc, IranMedex, SID, Cochrane library, Google Scholar, ProQuest, Scopus, Web of Science, and PubMed/Medline Embase with keywords: acute pancreatitis, chronic pancreatitis Hypercalcemia, parathyroid adenoma Primary hyperparathyroidism. Acute pancreatitis, chronic pancreatitis, hypercalcemia, primary hyperparathyroidism, and parathyroid adenoma were performed. The entry criteria were articles in English or Farsi, qualitative articles related to the objectives of the study. Exclusion criteria were articles that were in the form of posters, speeches, letters to the editor, and quantitative studies.

Results: The findings from the review of 20 qualitative studies showed that although the relationship between hypercalcemia caused by parathyroid adenoma and acute pancreatitis is a known medical phenomenon, it is very rare. Therefore, the pathophysiology of acute pancreatitis caused by hypercalcemia is not well understood, although some mechanisms have been suggested. Timely diagnosis of hypercalcemia and parathyroid adenoma surgery is the final treatment.

Conclusion: Acute pancreatitis is the first manifestation of a rare clinical symptom caused by hyperkalemia caused by hyperparathyroidism.

Keywords: Acute Pancreatitis, Chronic Pancreatitis, Hypercalcemia, Primary Hyperparathyroidism, Parathyroid Adenoma

Introduction

Pancreatitis is a disease caused by inflammation of the pancreas, which may be an acute process or a chronic disease.[1] There are various clinical situations that predispose to pancreatitis, and therefore, numerous causes of pancreatitis have been described, the most common of which are gallstone disease and alcoholism. Traditionally, 80% of acute pancreatitis (AP) cases are related to alcohol abuse and gallstone disease, and less than 10% have metabolic causes such as diabetic ketoacidosis, hypertriglyceridemia, and hypercalcemia with or without PHPT as a cause.[2] The prevalence of acute pancreatitis in PHPT is estimated between 1.5 and 13%. However, while some studies have shown an increased incidence of pancreatitis in patients with PHPT, others have not. Furthermore, the incidence of PHPT appears to be very rare among patients with pancreatitis. Three mechanisms have been described for the development of acute pancreatitis in patients with PHPT. One explanation is that PHPT-induced hypercalcemia leads to reactivation of trypsinogen to trypsin, leading to pancreatic autodigestion and subsequent pancreatitis. Another possibility is that hypercalcemia leads to the formation of pancreatic stones, ductal obstruction, and subsequent attacks of acute or chronic pancreatitis. Finally, factors other than calcium, such as genetic risk factors, may predispose patients with PHPT to acute pancreatitis.[3]

The first case report of AP in PHPT was published by Smith and Cook in 1940. Later, in 1980, a study by Bess et al.[4] from the Mayo Clinic that included 1153 patients with histopathologically confirmed PHPT showed that only 17 (1.5%) had previous or concurrent

pancreatitis. This frequency was comparable to the incidence of pancreatitis reported among hospitalized patients without PHPT. However, a link between the two diseases cannot be ruled out based on data from hospitals with a large number of symptomatic PHPT patients.

Primary hyperparathyroidism (PHPT) is usually characterized as an endocrine disorder with hypercalcemia attributed to overexpression of parathyroid hormone (PTH) from one or more parathyroid glands.[5] The occurrence of a hypercalcemic crisis is usually accompanied by an increase in PTH. Hypercalcemia in patients with PHPT can lead to various co-morbidities such as gastrointestinal symptoms, electrolyte disorders, kidney dysfunction, and acute or asymptomatic pancreatitis.[6,8]

Regulation of serum calcium in humans is mainly dependent on PTH secretion. Shepherd reported this association in Australia, where seven (5.1%) of 137 PHPT patients had pancreatic disease.[8] Western studies have shown the prevalence of pancreatitis in PHPT patients, which ranges from 5.1 to 8.1%.[8,9] However, Indian studies have reported a higher prevalence of AP in PHPT patients, ranging from 12.9 to 16%,[10] with almost equal numbers of CP and AP patients. Despite its rarity, the fact that parathyroidectomy has been shown to prevent recurrence of pancreatitis attacks suggests a causal relationship between these two diseases.[4,5]

Serum calcium plays an important role in the pathogenesis of pancreatitis. Three mechanisms have been proposed to cause AP in patients with PHPT. The first AP abnormalities occur within acinar cells. Calcium is the second most important intracellular messenger in acinar cells that initiates enzyme release through phosphorylation cascades. Elevated extracellular calcium levels due to PHPT may increase intracellular calcium signaling[11] and activate calcium-dependent proteins such as calcineurin as well as pancreatic proteases (especially trypsin) or activate NF-κB. It leads to the initiation of the pancreatic inflammatory cascade. In addition, hypercalcemia can lead to the formation of pancreatic stones, duct obstruction, and subsequent attacks of AP or CP.[12] Felderbauer et al. showed that PHPT patients with AP had a higher prevalence of mutations in serine protease inhibitor casal type 1 (SPINK-1), cystic fibrosis transmembrane conductance regulator (CFTR), and chymotrypsin C genes.[12]

The risk of pancreatitis is approximately 10-fold increased in PHPT, but pancreatitis rarely occurs. This suggests an existing but minor effect of hypercalcemia associated with PHPT. If pancreatitis occurs, it appears to be associated with genetic risk factors such as mutations in the SPINK1 and CFTR genes. In contrast, the combination of hypercalcemia and genetic variants in SPINK1 or CFTR increases the risk of pancreatitis in patients with pHPT.[13]

Materials and Methods

The current study is a qualitative systematic review based on the PRISMA model, which reviews the relationship between hyperkalemia, which is more related to hyperthyroidism, and pancreatitis based on articles published in domestic and foreign journals. This study was conducted in six stages.

The first stage of the research questions is what kind of relationship there can be and what other factors can have an effect on this relationship. In order to ask this question, the PICO strategy was used. P (population) patients who have pancreatitis due to hyperthyroidism. I (intervention), which is related to the discovery of the relationship between hypercalcemia and pancreatitis. C (comparion) was not used due to the type of review study. O (outcome) discovery of the relationship between hypercalcemia and pancreatitis.

The second stage was the selection of keywords related to the research topic and the search term and planning to determine the search strategies. It should be noted that descriptive terms and keywords were defined based on MESH based on the opinion of experts. The keywords are: hypercalcemia. Hyperparathyroidism. Pancreatitis Hyperthyroidism, Hyperthyroid, Thyrotoxicosis, Hypercalcemia, Pancreatitis The search strategies in PubMed are as follows: ("Pancreatitis"[Mesh]) AND "Hypercalcemia"[Mesh, Hypercalcemic AND hyperparathyroidism OR Thyrotoxicosis, (Pancreatitis [Title/Abstract]) AND (Hypercalcemia [Title/Abstract]).

In the third stage, the entry and exit criteria were determined by the members of the research team. The inclusion criteria are: 1: Related articles on the relationship between hypercalcemia and pancreatitis 2: Studies that were conducted from January 1, 2008, to January 2024. The choice of this 16-year period is because most of the studies conducted in this period are 3: Written in English and Persian. Articles that

were in the form of posters, speeches, or letters to the editor and were not related to the research objectives were excluded from the study.

The fourth stage was the systematic search of electronic databases. Scientific databases of academic Jihad, SID, Bank of Medical Science articles of Iran, IranDoc, international databases, PubMed, Web of Science, Google Scholar, from January 1st to January 2024, based on keywords and predetermined strategies, were searched. The fifth step was the selection of qualified research articles. The summaries of the articles were examined, and the screening of the studies and the extraction of the results, as well as the evaluation of the quality control of the articles, were evaluated. The related articles were separated, and their full text was extracted. A total of 24155 articles were found, and after removing duplicate articles, 1155 articles entered the review stage in terms of titles and abstracts. After reviewing the titles and abstracts of the articles, 100 articles entered the next stage, in which the full text of the articles was reviewed and the articles based on criteria exit and entry were checked. Finally, 20 articles were included in the final analysis.

In the sixth stage, the quality of the articles was checked. In order to check the quality of the articles, a checklist was prepared by Joanna Briggs to evaluate the quality of qualitative articles. This tool has ten questions that are divided into yes and no, unclear and not used. The purpose of this evaluation is to evaluate the methodological quality of the studies and the ways to achieve and find out the errors in the studies and the design, construction, and analysis of the data. Accordingly, 4 articles were excluded from the study due to poor quality. In order to control the risk of distortion, a search strategy with controlled keywords was used for each database, and studies were selected according to the inclusion and exclusion criteria. To answer the questions of a systematic review, the data extracted from the literature review were combined for the data extraction form was used to collect the data needed to answer the systematic review questions. The combination of data and their analysis was done descriptively.

After extraction, all the information collected from the qualitative studies was transcribed into a Word file, and the main and secondary themes were identified and coded, and the codes were compared, discussed, and interpreted.

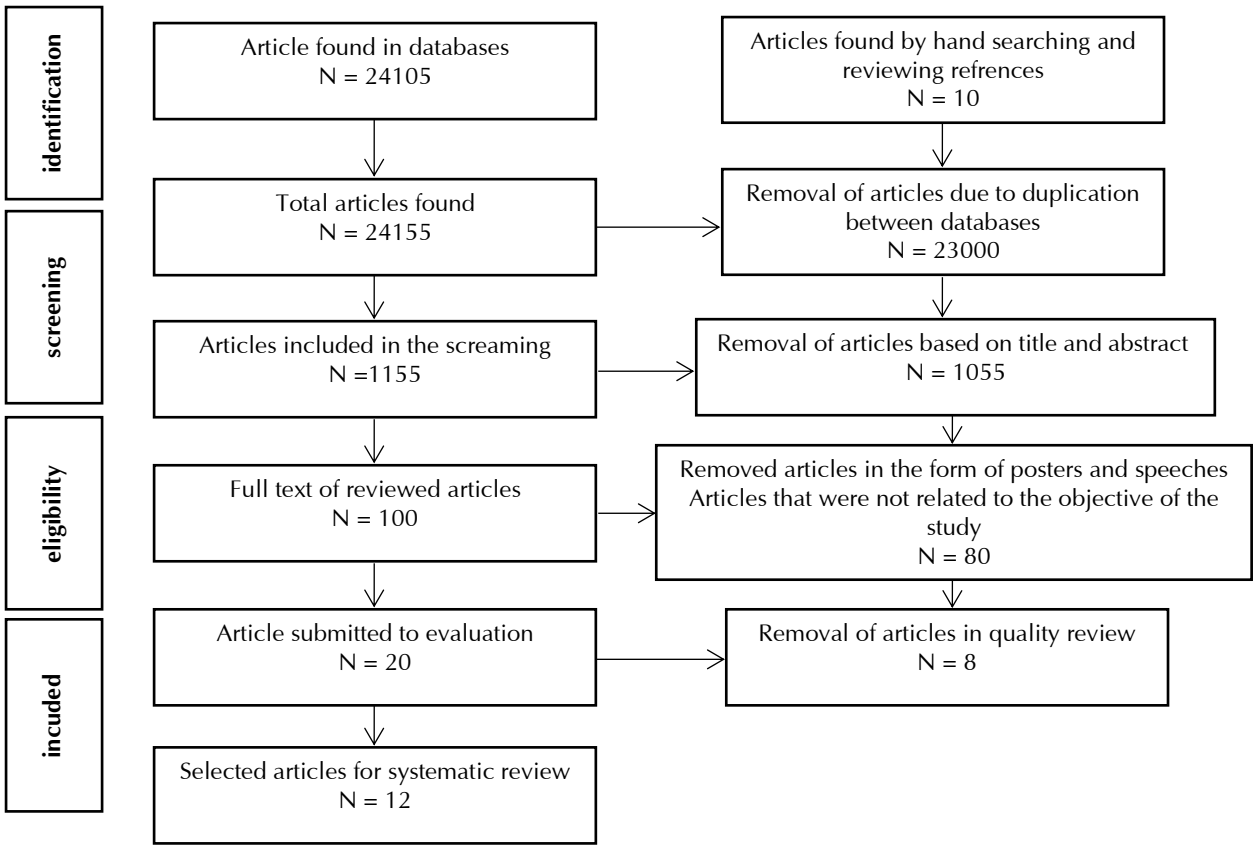

Figure1. Prisma Flow Diagram

Results	Title	Collection tool and type of qualitative study	Samples	Place of study	Year	Author name
Our results suggest that the association between acute pancreatitis and PHPT is a chance association and therefore acute pancreatitis should not be considered as an indication for parathyroid surgery.	Acute pancreatitis in primary hyperparathyroidism: a population-based study	The medical records linking system of Rochset Epidemiology Project	684 PHPT patients matched with 1364 control group	Olmsted County, Minnesota	2009	Teck Kim khoo et al
Pancreatitis should be an anticipated complication of PHPT and may be the only presenting complaint of PHPT. Early detection and removal of parathyroid lesions prevents recurrent attacks of AP and other complications associated with PHPT.	Primary hyperparathyroidism as acute pancreatitis: an institutional experience with literature review	A retrospective observation	۵۱patients PHPT	PHPT Registry from Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry	2022	Rashmi.KG et al
The risk of pancreatitis is approximately 10-fold increased in pHPT, but pancreatitis rarely occurs. This suggests an existing but minor effect of hypercalcemia associated with pHPT. If pancreatitis occurs, it appears to be associated with genetic risk factors such as mutations in the SPINK1 and CFTR genes. In contrast, the combination of hypercalcemia and genetic variants in SPINK1 or CFTR increases the risk of pancreatitis in patients with pHPT	Pancreatic risk in primary hyperparathyroidism with mutations in the trypsin inhibitor SPINK1 (N34S) and cystic fibrosis genes	Cohort study	۸۲۶patients with pancreatitis	St. Joseph's Hospital	2008	Peter felderbauer et al
Several lines of experimental evidence suggest that hypercalcemia can lead to intrapancreatic trypsin activation and pancreatic injury, and can predispose the pancreas to	Association of primary hyperparathyroidism with pancreatitis	retrospect	Patient with PHPT	Bill New Haven School of Medicine	2012	Harison x.bai et al 2012

pancreatitis. Pancreatitis in these conditions is likely the result of additional genetic and environmental influences. It is important to check serum calcium in cases of pancreatitis and to consider pancreatitis in PHPT patients presenting with abdominal symptoms						
The relationship between PHPT and pancreatitis is still a matter of debate. According to some studies, hypercalcemia is associated with different types of pancreatitis, including acute, subacute, and chronic pancreatitis. Prevention of more episodes of pancreatitis after parathyroidectomy supports this association.	Unusual presentation of primary hyperparathyroidism as recurrent pancreatitis: a case with a review of the literature	Case report	A 52-year-old patient	Sir sayajirao general hodpital	2023	Gaurav Mehta et al
In our study, the prevalence of pancreatitis in PHPT cases was 8.03%. Most of the patients were young. Normocalcemia was observed in 12 patients, so even if the calcium level is normal, PHPT should be suspected in young patients with pancreatitis. Parathyroidectomy resulted in complete resolution of pancreatitis symptoms in all 44 patients.	Pancreatitis and hyperthyroidism	A clinicopathological analysis	This clinicopathological profile of patients diagnosed with PHPT with pancreatitis in the Department of Endocrinology, SGPGI, Lucknow between 1989 and 2021	India	2024	Yuvraj Devgan et al
Despite the rarity of the association, a causal relationship is still suggested by the fact that parathyroidectomy appears to prevent recurrence of	Primary hyperthyroidism as recurrent acute pancreatitis: case report and literature review	Case report/systematic review	A patient	India	2011	Raiz a. Misgar et al

pancreatitis. Almost 100% improvement in pancreatitis symptoms has been reported after PHPT treatment.						
Parathyroidectomy may prevent recurrence of pancreatitis. Subsequent rapid hypocalcemia may develop, requiring calcium supplementation. A good collaboration between gastroenterologists, endocrinologists and surgeons is important in the treatment of this rare phenomenon of acute necrotizing pancreatitis due to hypercalcemia caused by PHPT.	Acute necrotizing pancreatitis as the first manifestation of primary hyperthyroidism	Case report	A patient	Belgium	2011	Jeroen I lenz et al
Patients with acute pancreatitis without a history of gallstone disease or alcohol use should be evaluated for other rare causes. Early diagnosis and prompt treatment of the underlying disease can prevent recurrence of pancreatitis.	Acute pancreatitis as an index manifestation of parathyroid adenoma	Case report	A patient	India	2021	M.sudharsha n et al
To our knowledge, this is the first case of moderate acute pancreatitis caused by primary hyperparathyroidis m with paraneoplastic syndrome. Although rare, hypercalcemia secondary to primary hyperparathyroidis m or malignancy usually appears in the advanced stage of malignancy and carries a poor prognosis	Acute pancreatitis with hypercalcemia due to primary hyperparathyroidis m with paraneoplastic syndrome: case report and literature review.	Case report/systematic review	A patient	Beijing	2021	Yang l ett al
Serum calcium was significantly higher in patients with PHPT with pancreatitis compared to those	Frequency and predictors of pancreatitis in symptomatic primary hyperparathyroidis	In this retrospective study, all consecutive patients with PHPT registered in the PHPT registry (www.indianphptregistry.com) from 20004 to 2013	218 patients	India	2018	Kumar arya et al

with PHPT without pancreatitis. A significant improvement in the symptoms related to pancreatitis was observed after therapeutic parathyroidectomy	m	were included in the study				
Pancreatitis is rare in hyperparathyroidism. Normal or higher calcemia during acute or chronic pancreatitis should always attract attention and be further investigated in search of an endocrine or malignant cause	Primary hyperparathyroidism and pancreatitis: a rare multifaceted association	Retrospective and descriptive study	5 patients	Spain	2016	I.Diallo et al

Results

PHPT is now a common endocrine disorder caused by an inappropriate overproduction of PTH secreted by an overactive parathyroid gland.[14] Compared to young people, postmenopausal women over 50 are more likely to suffer from PHPT.[15] The most common pathogenesis of PHPT is parathyroid adenoma (80-85%) and its rare causes include parathyroid hyperplasia, carcinoma, multiple endocrine neoplasia types 1 and 2A, and parathyroid cysts.[16] Most patients with PHPT have mild or no symptoms. Despite the variety of clinical manifestations of PHPT, hypercalcemia is the most common condition in most clinical cases.[18] Hypercalcemia is a common and potentially fatal metabolic disorder that is often attributed to PHPT, or malignancy-related disease.[19] PTH elevation is one of the main factors in the onset of hypercalcemia.

In a study by Teck Kim Khoo et al.,[15] our results show that the relationship between acute pancreatitis and PHPT is a chance relationship, and therefore acute pancreatitis should not be considered as an indication for parathyroid surgery. According to Rashmi.KG et al.,[31] pancreatitis should be an anticipated complication of PHPT and may be the only presenting complaint of PHPT. Early detection and removal of parathyroid lesions prevents recurrent attacks of AP and other complications associated with PHPT .

In a study by Peter Felderbauer et al.,[12] the risk of pancreatitis increases approximately 10 times in pHPT, but pancreatitis rarely occurs. This suggests an existing but minor effect of hypercalcemia associated with pHPT. If pancreatitis occurs, it appears to be associated with genetic risk factors such as mutations in the SPINK1 and CFTR genes. In contrast, the combination of hypercalcemia and genetic variants in SPINK1 or CFTR increases the risk of pancreatitis in patients with pHPT.

Harison x.Bai et al.[26] Several lines of experimental evidence show that hypercalcemia can lead to the activation of intrapancreatic trypsin and damage to the pancreas and can make the pancreas susceptible to pancreatitis. Pancreatitis in these conditions is likely the result of additional genetic and environmental influences. It is important to check serum calcium in cases of pancreatitis and to consider pancreatitis in PHPT patients presenting with abdominal symptoms.

In another study by Gaurav Mehta et al.,[30] the relationship between PHPT and pancreatitis is still a matter of debate. According to some studies, hypercalcemia is associated with different types of pancreatitis, including acute, subacute, and chronic pancreatitis. Prevention of more episodes of pancreatitis after parathyroidectomy supports this relationship.

In the study by Yuvraj Devgan et al.,[32] in our study, the prevalence of pancreatitis in PHPT cases was 8.03%. Most of the patients were young. Normocalcemia was observed in 12 patients, so even if the calcium level is normal, PHPT should be suspected in young patients with pancreatitis. Parathyroidectomy resulted

in complete resolution of pancreatitis symptoms in all 44 patients.

In a study by Raiz a. Misgar et al.,[22] despite the rarity of the association, a causal relationship is still suggested by the fact that parathyroidectomy seems to prevent recurrence of pancreatitis. Almost 100% improvement in pancreatitis symptoms has been reported after PHPT treatment.

In a study by Jeroen Lenz et al.,[33] parathyroidectomy may prevent recurrence of pancreatitis. Subsequent rapid hypocalcemia may develop, requiring calcium supplementation. A good collaboration between gastroenterologists, endocrinologists, and surgeons is important in the treatment of this rare phenomenon of acute necrotizing pancreatitis due to hypercalcemia caused by PHPT.

In a study by M. Sudharshan et al.,[34] patients with acute pancreatitis without a history of gallstone disease or alcohol consumption should be examined for other rare causes. Early diagnosis and prompt treatment of the underlying disease can prevent recurrence of pancreatitis.

In the study by Yang et al.,[28] to our knowledge, this is the first case of moderate acute pancreatitis caused by primary hyperparathyroidism with paraneoplastic syndrome. Although rare, hypercalcemia secondary to primary hyperparathyroidism or malignancy usually appears in the advanced stage of malignancy and carries a poor prognosis.

In a study by Kumar Arya et al.,[18] serum calcium was significantly higher in patients with PHPT with pancreatitis compared to those who had PHPT without pancreatitis. A significant improvement in the symptoms related to pancreatitis was observed after parathyroidectomy therapy.

In a study conducted by I. Diallo et al.,[30] the occurrence of pancreatitis in hyperparathyroidism is rare. Normal or higher calcemia during acute or chronic pancreatitis should always attract attention and be further investigated in search of an endocrine or malignant cause.

Discussion

This study was conducted with the aim of the relationship between pancreatitis and hypercalcemia. It shows in the studies conducted by Raize A. Misgar[22] and his colleagues. Despite its rarity, a causal relationship is still suggested by the fact that parathyroidectomy appears to prevent recurrence of pancreatitis. Almost 100% improvement in pancreatitis symptoms has been reported after PHPT treatment.

There are two mechanisms of pancreatitis caused by hypercalcemia. Hypercalcemia can lead to the reactivation of trypsinogen to trypsin, which leads to pancreatic autodigestion and subsequent pancreatitis. Another explanation is that hypercalcemia leads to the formation of pancreatic stones, duct obstruction, and subsequent attacks of acute or chronic pancreatitis. Also, genetic risk factors may predispose patients with PHPT to pancreatitis. Calcium levels probably play a role in the development of pancreatitis. Mean calcium values in patients with PHPT and pancreatic disease have been reported to be significantly higher than in patients with PHPT without pancreatic involvement. PHPT is associated with different types of pancreatitis, such as acute, subacute, or chronic calcifying pancreatitis.

In another study conducted by Jeroen Ilenz,[24] acute pancreatitis caused by hypercalcemia caused by PHPT is a rare disease. It was first described in 1957 by Cope et al.[16] Since then, the relationship between PHPT and pancreatitis has been questioned, but PHPT is now recognized as an accepted cause of pancreatitis. The prevalence of acute pancreatitis in patients with PHPT is estimated between 1.5 and 7%. Some studies have linked hyperparathyroidism to pancreatitis. however, the prevalence of acute pancreatitis in patients with PHPT does not differ from the general population. Therefore, there seems to be no direct causal relationship between PHPT and acute pancreatitis based on epidemiological data. However, it has been shown that hypercalcemia from any cause can lead to acute pancreatitis. When this combination occurs, pancreatitis is likely to be severe, and the degree of hypercalcemia may play an important role in this association. Three pathophysiological mechanisms have been proposed. Calcium deposits in the pancreatic duct may cause pancreatic duct obstruction.

In this study conducted by Ashuton Kumar Arya[18] and his colleagues, 16% of PHPT patients had pancreatitis. Of these, 51.4% have AP at the time of diagnosis. Western population studies have shown a prevalence of pancreatitis of 3.2-1.8% in patients with PHPT, but Indian studies have reported a higher prevalence (6.8-13%). Delay in diagnosis as well as variation in clinical presentation (symptomatic vs. asymptomatic) are possible explanations for the double

prevalence of pancreatitis in patients with PHPT in our and other Indian studies. In this study, 51.4% of PHPT patients with pancreatitis were male, which was consistent with previous studies. In a community-based study by Khoo et al.,[15] it was shown that the male-to-female ratio in PHPT with pancreatitis was similar to PHPT without pancreatitis (70% female, 30% male). No gender difference was observed between patients with acute PHPT and CP in this study. The gender representation of AP and CP in PHPT has not been previously reported. Abdominal pain was the most common clinical manifestation of PHPT with pancreatitis in our study (91.4%) and was also reported by others. In a study conducted by Yuvraj Devgan[32] and his colleagues, PHPT indicates an overproduction of non-physiological PTH. It is most commonly caused by a solitary parathyroid adenoma (80-85%), but less common causes include parathyroid hyperplasia, carcinoma, and MEN types 1 and 2A. Eirdheim was the first to report a case of PHPT and AP in 1903. Reported, when he noted necrotizing pancreatitis in a patient with parathyroid adenoma.[15] However, it was only in 1957 that Cope et al. wrote a seminal paper on pancreatitis as a presenting manifestation of PHPT. Since then, several individual cases and case series have been periodically reported, suggesting that concurrent hyperparathyroidism and pancreatitis are more than coincidental and that recurrent pancreatitis can be treated by treating the cause of the primary hyperparathyroidism. The largest series was reported by Mixter et al.[35]

They reported eleven cases of pancreatitis out of 155 cases of hyperparathyroidism at Massachusetts General Hospital between 1950 and 1962. These observations were later challenged by Bess and colleagues from the Mayo Clinic in 1980. They reviewed 1153 patients and showed that coexisting or history of pancreatitis was found in only 1.5% of patients, similar to the frequency of AP observed in the same control group. They suggested that the association may be coincidental rather than causal. Of 1153 patients with PHPT seen at the Mayobin Clinic between 1950 and 1975, only 17 (1.5%) had pancreatitis, a prevalence similar to that of a random hospital population. In addition, several of these patients had alternative explanations for pancreatitis. The same study concluded that it is generally difficult to draw correlations between the two disorders among hospitalized patients due to measurement bias. Because serum calcium was routinely measured in patients presenting with pancreatitis, they may be preferentially screened for PHPT compared to non-pancreatitis patients. Kho et al. reported that the estimated rate of AP development in PHPT was actually lower than in a randomly selected control group without PHPT. Among patients with PHPT, it was 114 per 100,000 person-years versus 140 per 100,000 person-years among controls. This study concluded that AP was not increased in community-dwelling patients with PHPT, and therefore, a causal relationship between PHPT and AP does not appear to exist. A strong argument against a causal relationship between PHPT and pancreatitis is that many patients with PHPT-related pancreatitis have been reported to have additional risk factors for pancreatitis. Much later, publications dealing with parathyroids showed an increase in the association of pancreatitis from 3.2 to 5.6 percent. Most of these patients present with mild hypercalcemia in the asymptomatic stage and undergo parathyroid surgery before they have a chance to develop pancreatitis. Similarly, other studies have reported that half of PHPT patients with pancreatitis have additional risk factors for AP. This could indicate that PHPT is a random association. On the other hand, it can show that multiple factors that cause pancreatitis are often necessary to develop the disease. The latter hypothesis explains why only a small number of patients with PHPT develop pancreatitis, meaning that they must receive one or more additional hits with PHPT to manifest the disease. However, in the present study, none of the PHPT cases had additional risk factors for pancreatitis. Among the studies that reported a positive association, four from India reported the highest rate of pancreatitis among patients with PHPT.

Mi et al.[31] reported the occurrence of pancreatitis in 12 of 51 people (23.5%). Bhadada et al. reported the incidence of pancreatitis in 35 of 218 subjects (16%). reported the occurrence of pancreatitis in 9 of 59 subjects (15%), while Jacob et al. reported it in 13 of 101 (13%) patients with PHPT. Nevertheless, pancreatitis appears to be 10 times more common in PHPT patients than in the population without parathyroid disease. This study suggests a strong causal relationship between PHPT and pancreatitis, as cases with additional risk factors for pancreatitis were excluded. None of the pancreatitis cases in our study had

additional risk factors for pancreatitis, such as gallstones, alcohol abuse, or hypertriglyceridemia. PHPT-pancreatitis appeared at a younger age with a predominance of men as opposed to women (27 of 44). In both studies, Carnaille et al.[36] From France and the study of Jacob et al.[10] from India, a lower age of presentation with a prevalence of pancreatitis was reported in men, which is consistent with our observations. The exact pathogenesis of this younger age, male presentation, and presence of skeletal/renal manifestations is less clear. A possible explanation could be the early detection of disease caused by AP at a relatively mild stage with a lower degree of elevation of intact PTH (i PTH). In addition, genetic risk factors for the development of AP may play a role in the younger age of presentation. The normal or elevated calcium levels observed in 12 patients may be because AP is well known to lower total serum calcium levels, underlying PHPT hypercalcemia may be masked, and the diagnosis may be missed. Unless serum calcium is measured again at follow-up. After the resolution of pancreatitis, our study is spread over a long period of time, so PTH levels have been estimated by different generations of assays over the years of use, and its effect on the correlation is not yet clear. According to the study by Smit et al.[37] in 2019, for classic PHPT, the type of PTH assay used does not affect diagnosis or management because the exact PTH concentration is less relevant. The American Association of Endocrine Surgeons guidelines for the management of PHPT do not address differences in PTH assays and do not provide recommendations on this issue. In contrast, the International Workshop on the Diagnosis of Asymptomatic PHPT considers differences in PTH assay measurements and recommends the use of assay-specific reference values. Generations of sensitivity assays have a similar diagnostic sensitivity for PHPT. Overestimation of PTH by second-generation assays in patients with hypercalcemic PHPT will be of minor consequence, as in these patients the distinction between hypercalcemia due to PTH overproduction and PTH-independent causes of hypercalcemia is clear. However, accurate measurement of PTH is important in identifying patients with primary normocalcemic hyperparathyroidism. Most studies conducted in India report the incidence between 6.8% and 12%. Parathyroidectomy resulted in complete resolution of pancreatitis symptoms in all 44 patients. It is suggested that parathyroid surgery should be performed before any pancreatic surgery due to its beneficial effect on the latter process, and acute episodes of pancreatitis should not be an obstacle for early surgery. The strengths of the study are the inclusion of a larger number of patients and a comprehensive clinical and biochemical evaluation.

Limitations include the retrospective nature of the study and lack of long-term follow-up. In a study conducted by Yang L and his colleagues,[28] it shows that acute pancreatitis is a common disease that is associated with significant complications and mortality. Alcoholic beverages and biliary diseases are the cause of almost all of these cases, with a prevalence of approximately 80 to 90 percent. In addition, uncommon causes include toxic substances, trauma, infection, autoimmune diseases, or metabolic disorders secondary to hypercalcemia, such as primary hyperparathyroidism or malignant tumors. In general, acute pancreatitis is associated with decreased serum calcium, but pancreatitis due to primary hyperparathyroidism or malignancy is usually associated with hypercalcemia. These two causes are rare in hypercalcemia. Although the relationship and pathophysiology are unclear, the association may not be coincidental. Inappropriate activation of digestive enzymes in the pancreas, especially trypsinogen in the acetabulum, may play an important role in the development of acute pancreatitis. An excessive increase in intracellular calcium concentration can lead to overactivation of digestive enzymes and blockage of the pancreatic ducts, causing pancreatic inflammatory secretion. Two rare but well-known causes of hypercalcemia have been discussed in the literature. Many cases of acute pancreatitis due to hyperparathyroidism with parathyroid adenoma or adenocarcinoma have been described. Regarding paraneoplastic syndromes, several cases have shown that pancreatitis is associated with Zollinger-Ellison syndrome. Four cases diagnosed as pancreatitis were associated with lung cancer. One case had pancreatic adenocarcinoma. One case with myelodysplastic syndromes eventually led to pancreatitis; one case had breast cancer. One case was associated with intraductal papillary neoplasm. Another case of Hodgkin's lymphoma with paraneoplastic hypercalcemic pancreatitis was reported. Two similar cases of pseudo-autoimmune pancreatitis with thymoma and myasthenia gravis were described. In addition, two rare cases of pancreatitis and ovarian carcinoma were reported, in which

pancreatitis was caused by female malignancies. Hyperparathyroidism is more at risk of acute pancreatitis. In the patient studied, examinations initially showed moderate to severe acute pancreatitis. It is from primary hyperparathyroidism. First, the main cause of acute pancreatitis includes alcohol consumption and gallstones, which were not present in this patient. Secondly, he had no family history of pancreatitis. In addition, PTH and serum calcium increased significantly, and treatment did not reduce refractory serum calcium. In addition, ultrasound and CT contrast of the neck showed nodules located at the junction of the left lobe of the thyroid and the parathyroid gland. Therefore, these findings suggest that the pathogenesis of acute pancreatitis is the result of hypercalcemia caused by hyperparathyroidism. Although no adenoma or adenocarcinoma was found, exploratory resection was performed for persistent serum calcium depletion. The pathological findings of the removed tissue suggest nodular goiter.

A review of the literature showed that some malignant tumors may secrete parathyroid hormone-related protein (PTHrP) instead of PTH and cause pancreatitis. The amino terminus of PTHrP has a similar structure to PTH. Both activate the PTH/PTHrP 1 receptor and reduce the renal clearance of calcium. In a study by L. Diallo et al.,[29] the incidence of pancreatitis secondary to PHPT is not so rare, with a prevalence of 3.6% (1.5 to 15.3%),[1] as with an 8% rate of this association in our study is shown. Our nosocomial prevalence of 1.25 cases per year suggests this rarity. The discovery of a pancreatic disease increases the risk of developing PHPT by 33, while the presence of PHPT increases the risk of pancreatitis by a factor of 10 to 30. However, some authors reject this increased risk of pancreatic disease with PHPT. Indeed, in the general population, they found a lower or equivalent prevalence of pancreatitis in patients with PHPT compared to controls. Pancreatitis occurs at an advanced stage of parathyroid disease, which explains the low prevalence of this association in developed countries, where PHPT occurs earlier is recognized. The mean age at diagnosis varies, but patients tend to be older than those with PHPT alone. In the cases described in India and Latin America, they are young middle-aged adults, whereas patients in the United States and France (60-70 years) were older. The male gender predominates in most studies with about 60-70% men, as opposed to patients with only one PHPT. Our series is characterized by only women with a mean age of 54 years. In CP, this mechanism seems to be evident before calcium deposits in the absence of other causes. Hypercalcemia acts by several mechanisms: increased calcium levels in the pancreatic juice in the origin of the activation of trypsinogen to trypsin. Activation of pancreatic enzymes through the lysosomal system and hydrolases. Calcium deposition and protein plug formation are responsible for upstream pancreatitis. A direct toxic effect of PTH on the pancreas has been noted, but pancreatitis is not usually found in dialysis patients with elevated PTH, and PTH is not higher in patients with pancreatitis during PHPT. A genetic risk factor has also been found. In fact, SPINK1 (inhibitor of serine protease Kazal type I) and CFTR (cystic fibrosis transmembrane conductance regulator) gene mutations were mostly found in patients with PHPT who developed AP. In our patients, hypercalcemia in all cases, despite pancreatitis, the mechanism looks original. Therefore, by observing these different mechanisms, the relationship between PHPT and pancreatitis can take different forms. Therefore, Yaqoub et al., proposed a classification of this association that could be of 4 forms: PHPT manifested by AP, PHPT manifested by recurrent AP without CP, PHPT manifested by CP with or without pancreatic calcification, or PHPT manifested by AP in the course Complicated postoperatively. In a study by Rashmi KG et al., experience with five PHPT-AP patients and findings from 111 other patients in the literature establish an etiological relationship between PHPT and AP, to Pancreatitis appears to be at least ten times more common in PHPT patients than in the general population.

PHPT-AP showed a male predominance at younger ages, in contrast to the female predominance seen in PHPT-NP. In both the study by Carnaille et al. from France and the study by Jacob et al. from India, a lower age of presentation was reported with the prevalence of AP in men, which is consistent with our observations. Abdominal pain was the most common (100%) clinical presentation of PHPT-AP in our study, and the same finding was reported by others. Skeletal manifestations such as bone pain and fractures were observed in only 20% and none of the PHPT-AP patients, respectively, which is lower than the similar prevalence among PHPT-NP patients (56.4% and 10.6%, respectively).

These observations are similar to those of Arya et al.[11] and Yadav et al. The exact pathogenesis of this lower age of presentation, male predominance, and the presence of skeletal/renal manifestations have not been established. A possible explanation could be the early diagnosis of AP disease at a relatively mild stage with a lower degree of iPTH elevation. In addition, genetic risk factors for developing AP can contribute to a younger age of presentation. One patient in the PHPT-AP group had a history of gallstones and was treated elsewhere for the same condition as AP before presenting to our institution. In the background of hypercalcemia and other complications related to PHPT, such as kidney stones, and the absence of evidence of kidney stones in the subsequent imaging with abdominal CT, the possibility of AP caused by hypercalcemia was considered in this patient.

Several studies have reported elevated serum calcium levels among PHPT patients with pancreatitis compared to patients with PHPT-NP. The results show that serum calcium levels above a threshold predispose PHPT patients to pancreatitis. However, in our study, PHPT patients with AP had serum calcium levels similar to PHPT patients without pancreatitis. At the time of presentation, normocalcemia was observed in 1 patient (20%), which can be attributed to calcium saponification in pancreatic tissue. The diagnosis of PHPT in this patient was suspected due to the absence of other risk factors for AP, and the patient was subsequently found to have elevated plasma iPTH levels. Therefore, a normal level of calcium at the time of presentation in patients with an acute episode of pancreatitis does not rule out the possibility of PHPT. The present study highlights the importance of measuring intact PTH levels and reassessing calcium levels in patients with unexplained AP. Because pancreatitis occurs primarily in patients with severe hypercalcemia, it is rarely associated with PHPT in developed countries where PHPT is diagnosed at a much earlier and milder stage. Serum ALP was significantly higher in PHPT-NP patients than in PHPT-AP patients, which was most likely due to more severe bone disease.

The limitations of this study are that it was not able to perform SPINK-1 and CFTR gene mutation analysis. Hence, the exact prevalence of genetic risk and idiopathic pancreatitis cannot be determined. In addition, the author mentions: We could not determine the reason for the lower frequency of renal manifestations in patients with PHPT-AP compared to patients with PHPT-NP, because due to the retrospective nature of this study, the information on urinary calcium profile It was not available for all patients. In a study conducted by Teck Kim Khoo and his colleagues,[15] it was shown. Half of these patients had other causes of acute pancreatitis: four patients with a potential cause of acute pancreatitis other than hypercalcemia, and a fifth patient who had been treated for PHPT 27 years before the onset of acute pancreatitis. Thus, the prevalence and incidence of acute pancreatitis in PHPT without an additional cause of acute pancreatitis may be less than half of what is reported here. In addition, the probability of developing acute pancreatitis in patients with PHPT was not higher than that of similar control patients in the community. These findings indicate that there is no causal relationship between PHPT and acute pancreatitis.

The results of this study contradict several reports that show that PHPT is a risk factor for the development of acute pancreatitis. Previous reports were mainly based on hospital diagnostic surgery groups, which probably select patients with more severe PHPT. In fact, patients in other studies had severe hypercalcemia, whereas in our group, serum calcium was only slightly elevated. Although some studies have shown that patients with PHPT and pancreatitis have higher calcium levels compared to patients with PHPT without pancreatitis, no significant relationship was found.

There are several limitations of this study that the researcher explains: Our study population is disproportionately white and slightly younger than the US population. Due to the retrospective nature of this study, we were also unable to specifically assess risk factors for acute pancreatitis. The special strength of this study is the comprehensive system of medical records in the Mayo Clinic. Therefore, details of nearly all medical care provided to residents of Olmsted County, Minnesota, are available for review. Finally, most patients with PHPT in the United States have mild asymptomatic hypercalcemia with typical characteristics of our community-based cohort, making our findings particularly relevant.

In conclusion, acute pancreatitis was observed in only 1.5% of community patients with PHPT, with an estimated incidence rate of 114 per 100,000 person-

years, similar to the frequency of acute pancreatitis, observed in matched controls. In addition, serum calcium level and PHPT status were not significantly related to the development of acute pancreatitis. We did not detect recurrent acute pancreatitis despite the fact that most patients with PHPT were observed. In patients with PHPT who developed acute pancreatitis, their disease had been present for an average of 11.4 years before its onset, and often other contributing causes were identified. Our results suggest that the association between acute pancreatitis and PHPT is a chance association, and therefore acute pancreatitis should not be considered as an indication for parathyroid surgery.

A study by Harrison x Bai et al.[26] shows that the strongest case against the association between PHPT and pancreatitis is from 2 reports from the Mayo Clinic in Rochester, MN. First, Bess et al. argue that it is generally difficult to establish an association between the two disorders among hospitalized patients due to measurement bias. Most cases of PHPT are asymptomatic until the late stage. In older reports from Western countries or recent reports from resource-limited areas, measurement of serum calcium was not part of the routine admission electrolyte profile. However, serum calcium was routinely performed in patients presenting with pancreatitis. Therefore, patients with pancreatitis may have been preferentially screened for PHPT compared to non-pancreatitis patients. In fact, 75% of patients (59 of 79) with PHPT were diagnosed with pancreatitis during labor.

The second main argument presented by Mayo reports is that 40% to 65% of PHPT-related pancreatitis cases had at least 1 concurrent cause for pancreatitis, such as gallstones, alcohol abuse, or elevated triglycerides. This could indicate that PHPT is a random association. Alternatively, it could indicate that multiple exposures that cause pancreatitis are often necessary to develop the disease. The latter hypothesis explains why only a small number of patients with PHPT develop pancreatitis. Meaning they must succumb to 1 hit with PHPT to manifest the disease. In line with a multiple-hit hypothesis for pancreatitis, Felderbauer et al.[12] assessed whether known pancreatitis-associated gene mutations were more common among PHPT patients with pancreatitis compared with non-pancreatitis PHPT patients. They showed that the former group had a higher frequency of casal serine protease inhibitor type 1, cystic fibrosis membrane conductance regulator, and possible chymotrypsin C mutations, although the latter finding was not statistically significant. Therefore, it appears that patients with PHPT may require multiple genetic and environmental influences to develop pancreatitis.

How might hypercalcemia predispose to pancreatitis?

Pancreatic parenchymal cell, acinar cell, is the primary site of onset of pancreatitis. It has been speculated that the calcium-sensing receptor (CaSR) may play a pathological role in the acinar cell during hypercalcemia. 31 CaSR is the dominant calcium sensor on the surface of principal cells of the parathyroid gland, which regulates PTH secretion in response to changes in serum calcium concentration. Patients with heterozygous loss-of-function mutations in CaSR develop a condition known as benign hypercalcemia, familial hypocalciuria. However, in the presence of hypercalcemia, it is not clear why they are generally thought to protect against pancreatitis. A new hypothesis is that CaSR expressed in the acinar cell is necessary to sensitize the acinar cell to extracellular calcium damage. Loss-of-function mutations may result in hypercalcemia due to defects in the parathyroid gland, but the same defect in acinar cell CaSR protects the patient from the deleterious effects of high calcium on the pancreas. If this assumption is correct, conversely, gain-of-function mutations in CaSR may predispose patients to pancreatitis, even in the setting of normocalcemia. Indeed, a few studies identified CaSR mutations in some patients with pancreatitis compared with control subjects. Two of the mutations may increase performance. Felderbauer and colleagues reported a R896H CaSR mutation in a chronic pancreatitis patient in combination with a serine protease inhibitor CaSR type 1 mutation. Stepanchick et al. recently showed that this mutation results in increased plasma membrane targeting of an otherwise functional CaSR, thus exhibiting a gain of function phenotype. Muddana et al. found that the R990G CaSR mutation was associated with chronic pancreatitis, particularly alcohol-related. This mutant appears to be more sensitive to calcium or calcium mimetics. The functional significance of CaSR mutations in the context of pancreatitis remains to be determined and may provide a clue to the unresolved question of how hypercalcemia may predispose to pancreatitis. However, CaSR mutations were not

increased in patients with PHPT and pancreatitis compared with PHPT without pancreatitis.

It is also possible that, independent of CaSR, elevated extracellular calcium leads to increased cytosolic calcium signaling. Trypsin in particular, or can activate NF-κB, leading to pancreatic inflammation and altered stress responses. Indeed, in experimental models, induction of acute hypercalcemia activates intrapancreatic trypsin. Furthermore, aberrant acinar calcium signals are observed in several forms of experimental pancreatitis.

Also, based on in vitro enzymatic studies, there are some notions that high cellular calcium may lead to increased calcium levels in intra-acinar vesicles, thereby preventing the autophagic degradation of trypsin directly or indirectly through another enzyme, such as chymotrypsin C.31. However, it is unclear whether the calcium dependence of pancreatic enzymes in isolated cell-free systems operates in cellular environments or whether the relatively small increase in extracellular calcium during hypercalcemia can directly affect those vesicular compartments. Therefore, hypercalcemia appears to cause pancreatic damage and possibly predispose patients with PHPT to pancreatitis, but the mechanism of calcium-induced damage is not clearly defined.[62]

In a study conducted by Gaurav Metha et al.,[30] three main mechanisms have been proposed in favor of the association between PHPT and pancreatitis: Hypercalcemia caused by PHPT causes excessive conversion of trypsinogen to trypsin in the pancreas and trypsin, which is an active protease. It causes auto-digestion of the pancreas and finally acute. Hypercalcemic pancreatitis causes an increase in the accumulation of calcium in the pancreatic ducts, which blocks them with the formation of pancreatic stones, which subsequently leads to pancreatitis. Increased calcium level along with some genetic mutations such as Serine Protease Inhibitor Casal Type 1 (SPINK1) and Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) increase the risk of pancreatitis in patients with PHPT. does not change Morbidity and mortality of acute pancreatitis is high. Therefore, pancreatitis should be treated first. Once the pancreatitis has resolved, parathyroidectomy should be performed, as surgery is the only treatment for symptomatic PHPT. A 95% recovery rate has been reported in PHPT after parathyroidectomy. Because parathyroidectomy may result in severe and prolonged hypocalcemia, also called "starved bone syndrome," blood calcium and PTH levels should be monitored regularly after surgery. As in our case, the patient may have osteolytic bone lesions without significant symptoms, and affected patients should be treated for bone loss.

Conflict of Interest

The authors declare no conflicts of interest.

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