World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i36.4063

World J Gastroenterol 2011 September 28; 17(36): 4063-4066
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Digestive manifestations of parathyroid disorders

Bassam Abboud, Ronald Daher, Joe Boujaoude

Bassam Abboud, Ronald Daher, Department of General Surgery, Hotel Dieu de France Hospital, Faculty of Medicine, Saint-Joseph University, Beirut 166830, Lebanon
Joe Boujaoude, Department of Gastroenterology, Hotel Dieu de France Hospital, Faculty of Medicine, Saint-Joseph University, Beirut 166830, Lebanon
Author contributions: Abboud B designed the research; Daher R, Abboud B and Boujaoude J performed the research; Daher R, Abboud B and Boujaoude J analyzed the data; Daher R and Abboud B wrote the paper.
Correspondence to: Bassam Abboud, MD, Department of General Surgery, Hotel Dieu de France Hospital, Alfred Naccache Street, Beirut 166830, Lebanon. dbabboud@yahoo.fr
Telephone: +961-1-615300 Fax: +961-1-615295
Received: December 29, 2010 Revised: March 25, 2011
Accepted: April 2, 2011
Published online: September 28, 2011

Key words: Dysparathyroidism; Hypoparathyroidism; Hyperparathyroidism; Digestive manifestations; Steatorrhea; Pancreatitis; Peptic ulcer

Peer reviewer: Dan L Dumitrascu, Professor, President, Romanian Society of Neurogastroenterology 2nd Medical Department University of Medicine and Pharmacy Iuliu Hatieganu Cluj, Romania

Abboud B, Daher R, Boujaoude J. Digestive manifestations of parathyroid disorders. *World J Gastroenterol* 2011; 17(36): 4063-4066 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i36/4063.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i36.4063

Abstract

The parathyroid glands are the main regulator of plasma calcium and have a direct influence on the digestive tract. Parathyroid disturbances often result in unknown long-standing symptoms. The main manifestation of hypoparathyroidism is steatorrhea due to a deficit in exocrine pancreas secretion. The association with celiac sprue may contribute to malabsorption. Hyperparathyroidism causes smooth-muscle atony, with upper and lower gastrointestinal symptoms such as nausea, heartburn and constipation. Hyperparathyroidism and peptic ulcer were strongly linked before the advent of proton pump inhibitors. Nowadays, this association remains likely only in the particular context of multiple endocrine neoplasia type 1/Zollinger-Ellison syndrome. In contrast to chronic pancreatitis, acute pancreatitis due to primary hyperparathyroidism is one of the most studied topics. The causative effect of high calcium level is confirmed and the distinction from secondary hyperparathyroidism is mandatory. The digestive manifestations of parathyroid malfunction are often overlooked and serum calcium level must be included in the routine workup for abdominal symptoms.

INTRODUCTION

The parathyroid glands play a major role in calcium homeostasis, and ultimately have an effect on all organs because of the complexity of intracellular calcium physiology. The gut and accessory organs are not spared. However, digestive manifestations of dysparathyroidism are not well known and typically rely on old articles and theories. This paper summarizes the digestive consequences of parathyroid disorders and highlights recent theories based on older studies.

DIGESTIVE MANIFESTATIONS OF HYPOPARATHYROIDISM

Hypoparathyroidism may be transient, genetically inherited, or acquired due to an autoimmune process. It may also be secondary to surgery or neck irradiation[1]. Digestive manifestations of hypoparathyroidism are few and consist mainly of steatorrhea.

Steatorrhea related to hypoparathyroidism is a consequence of bilio-pancreatic exocrine deficit due to insufficient meal-stimulated cholecystokinin secretion by the

duodenal mucosa[2]. The treatment of fat malabsorption in idiopathic hypoparathyroidism comprises: medium-chain triglycerides diet[3], correction of hypoparathyroidism, administration of vitamin D[4], and normalization of hypocalcemia[5]. In contrast, secondary hyperparathyroidism, as a consequence of malabsorption and steatorrhea, is accompanied by normal or sub-normal serum calcium level.

Idiopathic hypoparathyroidism can be associated with other digestive autoimmune diseases that may cause diarrhea. Few reports have been published on the coexistence of primary hypoparathyroidism and celiac disease[6-8]. Kumar *et al*[9] have explored this association in a cross-reactive immunological pathway. If suspected by resistance to vitamin D supplementation[10], the coexistence of celiac sprue must be ruled out by duodenal biopsy. In such cases, gluten-free diet should be included in the treatment regimen[11,12]. Moreover, in the specific context of celiac sprue, Parathyroid hormone (PTH) level might not be elevated because of parathyroid atrophy, and secondary hyperparathyroidism might not appear[13]. Finally, since its description by Reisner *et al*[14] more than 50 years ago, the coexistence of idiopathic hypoparathyroidism and pernicious anemia has not been further reported.

DIGESTIVE MANIFESTATIONS OF HYPERPARATHYROIDISM

The gastrointestinal manifestations of primary hyperparathyroidism (PHPT) have been described many decades ago[15]. Truly asymptomatic hyperparathyroidism is rare when thorough anamnesis looks for subtle symptoms. Most frequent digestive manifestations are constipation, heartburn, nausea and appetite loss that occur in 33%, 30%, 24% and 15% of cases, respectively[16]. Significant reduction in symptom rates is found after parathyroidectomy. Vague abdominal pain can be as frequent as 29%[17]. The exact pathophysiological mechanism is not fully understood. Alterations in gene expression secondary to sustained stimulation of PTH receptors may help explain the symptoms[18]. As a result, gut atony occurs and leads to constipation in the colon and dyspepsia in the stomach[17]. Finally, PHPT has been associated with increased incidence of malignancies, especially of the colon[19].

The association between PHPT and peptic ulcer disease is a yet-to-be-resolved issue. Most studies about this subject date were performed several decades ago[18,20-23], did not include prospective large-scale studies, and led to controversial results. Compared to 30% in adults with hyperparathyroidism[18], peptic ulcer was found in 5% of autopsies in the general population before the advent of the proton pomp inhibitors[20]. Other studies have reported results between these two extremes[21]. On the other hand, among patients with duodenal ulcer, Frame *et al*[22] have shown a 10-fold increase in the incidence of PHPT. As reported in old studies, complete correlation between hyperparathyroidism and increased gastric acid secretion could not be found, and normalization of the latter was not systematic after parathyroidectomy[21,23-28]. Again, the correlation between hypergastrinemia and hyperparathyroidism was not constant throughout previous studies[28,29], although Reeder *et al*[30] have found a direct calcium-to-gastric hypersecretion relationship in hypergastrinemia. The only prospective study conducted by Corleto *et al*[31] failed to confirm these findings. Zollinger-Ellison syndrome (ZES) may coexist with PHPT in the context of multiple endocrine neoplasia type 1. In a prospective study, Norton *et al*[32] reported a significant biochemical improvement of ZES in 20% of patients who underwent resection of more than three parathyroid glands. Finally, pancreatic polypeptide was once correlated with hyperparathyroidism[33].

Acute pancreatitis caused by PHPT was first described by Cope *et al*[34] in 1957. Since that date, the exact relationship between these two entities has been questioned, until PHPT was accepted as an etiology for pancreatitis[35]. Incidence of acute pancreatitis in patients with PHPT has varied from 1%[36] to 12%[37] in retrospective series, with intermediate values[38,39]. Jacob *et al*[40] have shown a 28-fold increased risk of pancreatitis in hyperparathyroid patients compared to the general population. After eliminating all other causes, mean plasma calcium level seems to be the only predictive factor for pancreatitis development[37,40,41]. Its dosage must be included in the etiological work-up, although hyperparathyroidism is found in < 1% of patients who present with acute pancreatitis[42]. Carnaille *et al*[37] have shown that most patients had single adenoma, which suggested that pancreatitis was a consequence (and not the cause) of hyperparathyroidism. Additionally, acute pancreatitis may be the presenting form of PHPT[38,43,44], even in its ectopic localization[45,46]. In contrast, Felderbauer *et al*[39] have stressed that genetic mutations constitute a greater risk factor for pancreatitis than serum calcium.

The pathophysiological mechanism that leads to pancreatitis seems more related to hypercalcemia than to PHPT. It has been shown that hypercalcemia from any cause can lead to pancreatitis[47-49]. As confirmed by experimental studies, calcium ions cause calculus deposition within the pancreatic ductules, with consequent obstruction and inflammation[50]. Moreover, calcium can trigger the pancreatitis cascade by promoting conversion of trypsinogen to trypsin[51,52].

Interrelation between acute pancreatitis and parathyroid function can be summarized as follows: (1) acute pancreatitis results in a tendency to hypocalcemia and secondary hyperparathyroidism[53,54]. Compensation need is correlated to pancreatitis severity as shown by PTH level[55]; (2) severe and/or complicated pancreatitis can lead to overt hypocalcemia through relative deficiency in PTH secretion[54], because exogenous administration of PTH normalizes calcium level[56]; (3) in severe pancreatitis, resistance to PTH action in bones and kidneys may occur because of fluid sequestration and reduction in efficient arterial blood volume[53]; (4) once the diagnosis of PHPT-induced acute pancreatitis is established, parathyroidectomy is mandatory because it prevents recurrence[37,42].

Bhadada *et al*[57] have studied PHPT-induced chronic pancreatitis and compared it to pancreatitis of other causes. PTH and calcium levels are significantly more elevated in PHPT, while in others, elevated PTH level is secondary to maintain normocalcemia. With regard to complications, it seems that chronic pancreatitis secondary to PHPT does not differ from chronic pancreatitis of other causes. This entity needs to be studied by larger studies for further understanding.

In conclusion, serum calcium level must be considered among the usual tests in patients with rare and/or non-specific abdominal symptoms. Hypoparathyroidism mainly manifests in the gut as malabsorptive diarrhea. Laboratory tests are essential for the diagnosis of secondary hypocalcemia when treatment is medical. PHPT causes non-specific digestive symptoms that are consequent to smooth-muscle atony. Association of peptic ulcer with PHPT is not as clear as described by old literature except for ZES in MEN 1. In contrast, PHPT is a confirmed risk factor for acute pancreatitis that can be its presenting form. Finally, PHPT-induced chronic pancreatitis needs further study for confirmation.

REFERENCES

1 **Maeda SS**, Fortes EM, Oliveira UM, Borba VC, Lazaretti-Castro M. Hypoparathyroidism and pseudohypoparathyroidism. *Arq Bras Endocrinol Metabol* 2006; **50**: 664-673
2 **Heubi JE**, Partin JC, Schubert WK. Hypocalcemia and steatorrhea--clues to etiology. *Dig Dis Sci* 1983; **28**: 124-128
3 **Lorenz R**, Burr IM. Idiopathic hypoparathyroidism and steatorrhea: a new aid in management. *J Pediatr* 1974; **85**: 522-525
4 **Clarkson B**, Kowlessar OD, Horwith M, Sleisenger MH. Clinical and metabolic study of a patient with malabsorption and hypoparathyroidism. *Metabolism* 1960; **9**: 1093-1106
5 **Peracchi M**, Bardella MT, Conte D. Late-onset idiopathic hypoparathyroidism as a cause of diarrhoea. *Eur J Gastroenterol Hepatol* 1998; **10**: 163-165
6 **Wortsman J**, Kumar V. Case report: idiopathic hypoparathyroidism co-existing with celiac disease: immunologic studies. *Am J Med Sci* 1994; **307**: 420-427
7 **Frysák Z**, Hrcková Y, Rolinc Z, Hermanová Z, Lukl J. [Idiopathic hypoparathyroidism with celiac disease--diagnostic and therapeutic problem]. *Vnitr Lek* 2000; **46**: 408-412
8 **Gelfand IM**, DiMeglio LA. Hypocalcemia as a presenting feature of celiac disease in a patient with DiGeorge syndrome. *J Pediatr Endocrinol Metab* 2007; **20**: 253-255
9 **Kumar V**, Valeski JE, Wortsman J. Celiac disease and hypoparathyroidism: cross-reaction of endomysial antibodies with parathyroid tissue. *Clin Diagn Lab Immunol* 1996; **3**: 143-146
10 **Marcondes JA**, Seferian Junior P, Mitteldorf CA. Resistance to vitamin D treatment as an indication of celiac disease in a patient with primary hypoparathyroidism. *Clinics* (Sao Paulo) 2009; **64**: 259-261
11 **Isaia GC**, Casalis S, Grosso I, Molinatti PA, Tamone C, Sategna-Guidetti C. Hypoparathyroidism and co-existing celiac disease. *J Endocrinol Invest* 2004; **27**: 778-781
12 **Matsueda K**, Rosenberg IH. Malabsorption with idiopathic hypoparathyroidism responding to treatment for coincident celiac sprue. *Dig Dis Sci* 1982; **27**: 269-273
13 **Jorde R**, Saleh F, Sundsfjord J, Haug E, Skogen B. Coeliac disease in subjects with secondary hyperparathyroidism. *Scand J Gastroenterol* 2005; **40**: 178-182
14 **Reisner DJ**, Ellsworth RM. Coexistent idiopathic hypoparathyroidism and pernicious anemia in a young girl: case report. *Ann Intern Med* 1955; **43**: 1116-1124
15 **St Goar WT**. Gastrointestinal symptoms as a clue to the diagnosis of primary hyperparathyroidism: a review of 45 cases. *Ann Intern Med* 1957; **46**: 102-118
16 **Chan AK**, Duh QY, Katz MH, Siperstein AE, Clark OH. Clinical manifestations of primary hyperparathyroidism before and after parathyroidectomy. A case-control study. *Ann Surg* 1995; **222**: 402-412; discussion 412-414
17 **Gardner EC**, Hersh T. Primary hyperparathyroidism and the gastrointestinal tract. *South Med J* 1981; **74**: 197-199
18 **Ellis C**, Nicoloff DM. Hyperparathyroidism and peptic ulcer disease. *Arch Surg* 1968; **96**: 114-118
19 **Sharma S**, Longo WE, Baniadam B, Vernava AM. Colorectal manifestations of endocrine disease. *Dis Colon Rectum* 1995; **38**: 318-323
20 **Ellison EH**, Abrams JS, Smith DJ. A postmortem analysis of 812 gastroduodenal ulcers found in 20,000 consecutive autopsies, with emphasis on associated endocrine disease. *Am J Surg* 1959; **97**: 17-30
21 **Ostrow JD**, Blanshard G, Gray SJ. Peptic ulcer in primary hyperparathyroidism. *Am J Med* 1960; **29**: 769-779
22 **Frame B**, Haubrich WS. Peptic ulcer and hyperparathyroidism: a survey of 300 ulcer patients. *Arch Intern Med* 1960; **105**: 536-541
23 **Barreras RF**, Donaldson RM. Role of calcium in gastric hypersecretion, parathyroid adenoma and peptic ulcer. *N Engl J Med* 1967; **276**: 1122-1124
24 **McGuigan JE**, Colwell JA, Franklin J. Effect of parathyroidectomy on hypercalcemic hypersecretory peptic ulcer disease. *Gastroenterology* 1974; **66**: 269-272
25 **Ward JT**, Adesola AO, Welbourn RB. The parathyroids, calcium and gastric secretion in man and the dog. *Gut* 1964; **5**: 173-183
26 **Segawa K**, Nakazawa S, Naito Y, Imai K, Yamase H, Yamada K, Yamamoto T, Ichikawa M, Hidano H, Kachi T, Hayashi S, Kawaguchi S, Tsukamoto Y, Kajikawa M, Kimoto E, Ichikawa T. The further investigation on the gastric acid secretion in the primary hyperparathyroidism. *Gastroenterol Jpn* 1977; **12**: 347-351
27 **Patterson M**, Wolma F, Drake A, Ong H. Gastric secretion and chronic hyperparathyroidism. *Arch Surg* 1969; **99**: 9-14
28 **Wilson SD**, Singh RB, Kalkhoff RK. Does hyperparathyroidism cause hypergastrinemia? *Surgery* 1976; **80**: 231-237
29 **Wesdorp RI**, Wang CA, Hirsch H, Fischer JE. Plasma and parathyroid tumor tissue gastrin and hyperparathyroidism. *Am J Surg* 1976; **131**: 60-63
30 **Reeder DD**, Jackson BM, Ban J, Clendinnen BG, Davidson WD, Thompson JC. Influence of hypercalcemia on gastric secretion and serum gastrin concentrations in man. *Ann Surg* 1970; **172**: 540-546
31 **Corleto VD**, Minisola S, Moretti A, Damiani C, Grossi C, Ciardi S, D'Ambra G, Bordi C, Strom R, Spagna G, Delle Fave G, Annibale B. Prevalence and causes of hypergastrinemia in primary hyperparathyroidism: a prospective study. *J Clin Endocrinol Metab* 1999; **84**: 4554-4558
32 **Norton JA**, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK, Marx SJ, Gibril F, Jensen RT. Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia-type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. *Ann Surg* 2008; **247**: 501-510
33 **Strodel WE**, Vinik AI, Eckhauser FE, Thompson NW. Hyperparathyroidism and gastroenteropancreatic hormone levels. *Surgery* 1985; **98**: 1101-1106
34 **Cope O**, Culver PJ, Mixter CG, Nardi GL. Pancreatitis, a diagnostic clue to hyperparathyroidism. *Ann Surg* 1957; **145**: 857-863
35 **Banks PA**, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379-2400
36 **Bess MA**, Edis AJ, van Heerden JA. Hyperparathyroidism

and pancreatitis. Chance or a causal association? *JAMA* 1980; **243**: 246-247
37 **Carnaille B**, Oudar C, Pattou F, Combemale F, Rocha J, Proye C. Pancreatitis and primary hyperparathyroidism: forty cases. *Aust N Z J Surg* 1998; **68**: 117-119
38 **Shepherd JJ**. Hyperparathyroidism presenting as pancreatitis or complicated by postoperative pancreatitis. *Aust N Z J Surg* 1996; **66**: 85-87
39 **Felderbauer P**, Karakas E, Fendrich V, Bulut K, Horn T, Lebert R, Holland-Letz T, Schmitz F, Bartsch D, Schmidt WE. Pancreatitis risk in primary hyperparathyroidism: relation to mutations in the SPINK1 trypsin inhibitor (N34S) and the cystic fibrosis gene. *Am J Gastroenterol* 2008; **103**: 368-374
40 **Jacob JJ**, John M, Thomas N, Chacko A, Cherian R, Selvan B, Nair A, Seshadri M. Does hyperparathyroidism cause pancreatitis? A South Indian experience and a review of published work. *ANZ J Surg* 2006; **76**: 740-744
41 **Curto C**, Caillard C, Desurmont T, Sebag F, Brunaud L, Kraimps JL, Hamy A, Mathonnet M, Bresler L, Henry JF, Mirallié E. [Acute pancreatitis and primary hyperparathyroidism: a multicentric study by the Francophone Association of Endocrine Surgeons]. *J Chir* (Paris) 2009; **146**: 270-274
42 **Prinz RA**, Aranha GV. The association of primary hyperparathyroidism and pancreatitis. *Am Surg* 1985; **51**: 325-329
43 **Lenz JI**, Jacobs JM, Op de Beeck B, Huyghe IA, Pelckmans PA, Moreels TG. Acute necrotizing pancreatitis as first manifestation of primary hyperparathyroidism. *World J Gastroenterol* 2010; **16**: 2959-2962
44 **He JH**, Zhang QB, Li YM, Zhu YQ, Li X, Shi B. Primary hyperparathyroidism presenting as acute gallstone pancreatitis. *Chin Med J* (Engl) 2010; **123**: 1351-1352
45 **Imachi H**, Murao K, Kontani K, Yokomise H, Miyai Y, Yamamoto Y, Kushida Y, Haba R, Ishida T. Ectopic mediastinal parathyroid adenoma: a cause of acute pancreatitis. *Endocrine* 2009; **36**: 194-197
46 **Foroulis CN**, Rousogiannis S, Lioupis C, Koutarelos D, Kassi G, Lioupis A. Ectopic paraesophageal mediastinal parathyroid adenoma, a rare cause of acute pancreatitis. *World J Surg Oncol* 2004; **2**: 41
47 **Brandwein SL**, Sigman KM. Case report: milk-alkali syndrome and pancreatitis. *Am J Med Sci* 1994; **308**: 173-176
48 **Gafter U**, Mandel EM, Har-Zahav L, Weiss S. Acute pancreatitis secondary to hypercalcemia. Occurrence in a patient with breast carcinoma. *JAMA* 1976; **235**: 2004-2005
49 **Hochgelerent EL**, David DS. Acute pancreatitis secondary to calcium infusion in a dialysis patient. *Arch Surg* 1974; **108**: 218-219
50 **Ward JB**, Petersen OH, Jenkins SA, Sutton R. Is an elevated concentration of acinar cytosolic free ionised calcium the trigger for acute pancreatitis? *Lancet* 1995; **346**: 1016-1019
51 **Mithöfer K**, Fernández-del Castillo C, Frick TW, Lewandrowski KB, Rattner DW, Warshaw AL. Acute hypercalcemia causes acute pancreatitis and ectopic trypsinogen activation in the rat. *Gastroenterology* 1995; **109**: 239-246
52 **Frick TW**, Fernández-del Castillo C, Bimmler D, Warshaw AL. Elevated calcium and activation of trypsinogen in rat pancreatic acini. *Gut* 1997; **41**: 339-343
53 **Hauser CJ**, Kamrath RO, Sparks J, Shoemaker WC. Calcium homeostasis in patients with acute pancreatitis. *Surgery* 1983; **94**: 830-835
54 **Condon JR**, Ives D, Knight MJ, Day J. The aetiology of hypocalcaemia in acute pancreatitis. *Br J Surg* 1975; **62**: 115-118
55 **McKay C**, Beastall GH, Imrie CW, Baxter JN. Circulating intact parathyroid hormone levels in acute pancreatitis. *Br J Surg* 1994; **81**: 357-360
56 **Robertson GM**, Moore EW, Switz DM, Sizemore GW, Estep HL. Inadequate parathyroid response in acute pancreatitis. *N Engl J Med* 1976; **294**: 512-516
57 **Bhadada SK**, Udawat HP, Bhansali A, Rana SS, Sinha SK, Bhasin DK. Chronic pancreatitis in primary hyperparathyroidism: comparison with alcoholic and idiopathic chronic pancreatitis. *J Gastroenterol Hepatol* 2008; **23**: 959-964

S- Editor Sun H **L- Editor** Kerr C **E- Editor** Xiong L