

2019

## Primary hyperparathyroidism can generate recurrent pancreatitis and secondary diabetes mellitus – A case report

Nicoleta Mîndrescu

Georgeta Văcaru

Emil Ștefănescu

Loreta Guja

Rucsandra Elena Dănciulescu Miulescu

Follow this and additional works at: <https://scholar.valpo.edu/jmms>

 Part of the [Endocrinology, Diabetes, and Metabolism Commons](#), [Gastroenterology Commons](#), and the [Internal Medicine Commons](#)

---

### Recommended Citation

Mîndrescu, Nicoleta; Văcaru, Georgeta; Ștefănescu, Emil; Guja, Loreta; and Dănciulescu Miulescu, Rucsandra Elena (2019) "Primary hyperparathyroidism can generate recurrent pancreatitis and secondary diabetes mellitus – A case report," *Journal of Mind and Medical Sciences*: Vol. 6 : Iss. 2 , Article 26.

DOI: 10.22543/7674.62.P361366

Available at: <https://scholar.valpo.edu/jmms/vol6/iss2/26>

This Case Presentation is brought to you for free and open access by ValpoScholar. It has been accepted for inclusion in Journal of Mind and Medical Sciences by an authorized administrator of ValpoScholar. For more information, please contact a ValpoScholar staff member at [scholar@valpo.edu](mailto:scholar@valpo.edu).



Received for publication: July 06, 2019  
Accepted: September 02, 2019

## Case report

# Primary hyperparathyroidism can generate recurrent pancreatitis and secondary diabetes mellitus – A case report

Nicoleta Mîndrescu<sup>1</sup>, Georgeta Văcaru<sup>2</sup>, Emil Ștefănescu<sup>3</sup>, Loreta Guja<sup>3</sup>, Rucsandra Elena Dănciulescu Miulescu<sup>3,4</sup>

<sup>1</sup>Nicodiab Private Practice, Bucharest, Romania

<sup>2</sup>EasyDiet Private Practice, Bucharest, Romania

<sup>3</sup>Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

<sup>4</sup>N.C. Paulescu National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

### Abstract

*Introduction.* Acute or recurrent pancreatitis may be a complication of primary hyperparathyroidism and patients with previous episodes of pancreatitis may develop secondary diabetes mellitus. *Case report.* We describe the clinical case of a 52-year old Caucasian man diagnosed with chronic recurrent pancreatitis in 2007. The first episode of acute pancreatitis occurred in 2002, followed by another 4 episodes in 2004 and 2007. In 2004, papilofincterectomy was implemented with a stent mount that was removed one month later. In 2005, the patient underwent a surgical intervention for the diagnosis of chronic lithiasis, and cholecystectomy was performed. Additional investigations on the etiology of recurrent chronic pancreatitis, initially diagnosed as idiopathic, revealed elevated values of total serum calcium, serum parathormone, and the presence of a parathyroid adenoma in the right lower pole of the thyroid. In September 2007, parathyroidectomy was performed with a favorable evolution and the remission of the acute pancreatitis episodes. The patient had not had any family history of diabetes; in 2017 he was diagnosed with diabetes. *Conclusion.* In cases of recurrent pancreatitis, screening for hyperparathyroidism is recommended. Metabolic evaluation is required, because the risk of developing diabetes in patients with recurrent pancreatitis is high.

### Keywords

: primary hyperparathyroidism, recurrent pancreatitis, secondary diabetes mellitus

### Highlights

- ✓ In cases of recurrent renal lithiasis or pancreatitis, screening for hyperparathyroidism is recommended.
- ✓ Metabolic evaluation is required in patients with recurrent pancreatitis because of their high risk of developing diabetes.

**To cite this article:** Nicoleta Mîndrescu, Georgeta Văcaru, Emil Ștefănescu, Loreta Guja, Rucsandra Elena Dănciulescu Miulescu. Primary hyperparathyroidism can generate recurrent pancreatitis and secondary diabetes mellitus – A case report. *J Mind Med Sci.* 2019; 6(2): 361-366. DOI: 10.22543/7674.62.P361366



\*Corresponding author: Rucsandra Elena Dănciulescu Miulescu, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania  
E-mail: [rucsandra\\_m@yahoo.com](mailto:rucsandra_m@yahoo.com)

## Introduction

Primary hyperparathyroidism is an endocrine disorder generated by the autonomous production of parathyroid hormone (PTH). The prevalence of the disease varies between 0.1% and 1.0 %, being the third endocrine disease after diabetes and thyroid disorder. The affliction is generated in most situations by a solitary parathyroid adenoma. Other causes of primary hyperparathyroidism include: multiple adenoma, hyperplasia of the four glands, and parathyroid carcinoma (1). PTH acts on the bones, kidneys, and small intestine. In the bones, PTH stimulates osteoblasts directly and osteoclasts indirectly, which leads to the release of calcium secondary to the resorption of the bones. The effects of PTH on the kidneys include: increased calcium reabsorption and decreased phosphate reabsorption; and activation of the  $1\alpha$  hydroxylase, an enzyme that catalyzes the transformation of 25-hydroxycholecalciferol (the inactive form of vitamin D) to 1,25-dihydroxycholecalciferol (the active form of vitamin D). In the small intestine, the active form of vitamin D ensures the absorption of calcium through two pathways: active transcellular and passive paracellular pathway (2, 3). The consequences of primary hyperparathyroidism are hypercalcemia (but the normocalcemic variant is now recognized), hypercalciuria, hypophosphatemia, damage of the cortical and trabecular bones, renal, gastrointestinal, cardiovascular, neuromuscular, and psychiatric symptoms. The clinical form includes symptomatic or asymptomatic diseases. Symptomatic primary hyperparathyroidism occurs in countries where biochemical screenings are not routinely used (4). The introduction of the serum AutoAnalyzer in 1970 allowed the identification of patients with asymptomatic hypercalcemia, and advances in techniques to determine PTH have facilitated the diagnosis of primary hyperparathyroidism (5).

Acute or recurrent pancreatitis may be a complication of primary hyperparathyroidism (6, 7). The prevalence of acute or recurrent pancreatitis in patients with primary hyperparathyroidism has been estimated, according to some studies, between 1.5% and 13% (5). A study published in 2009 by Khoo and collaborators contradicts previous reports. Their study included 684 patients with primary hyperparathyroidism. 10 patients (1.5%) developed acute pancreatitis compared to 32 out of the 1,368 (2.3%) from the control group. The authors concluded that there is no causal relationship between primary hyperparathyroidism and acute pancreatitis (8).

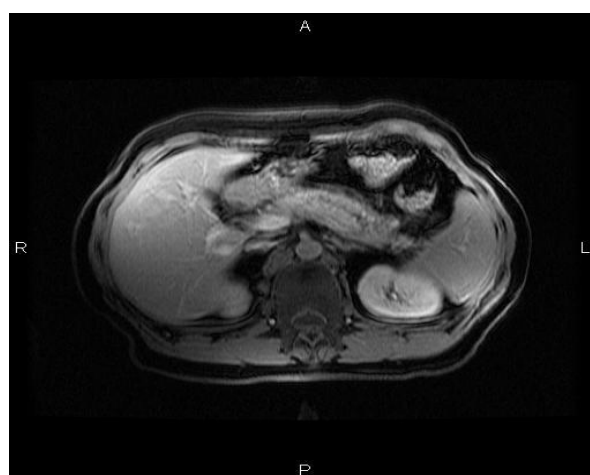
Subjects with previous episodes of pancreatitis may develop diabetes mellitus. The prevalence of diabetes secondary to pancreatitis is estimated between 5% and 10%

in the Western population (9, 10). In 2013, Ewald and Bretzel suggested several diagnostic criteria for diabetes mellitus secondary to pancreatic diseases, as follows:

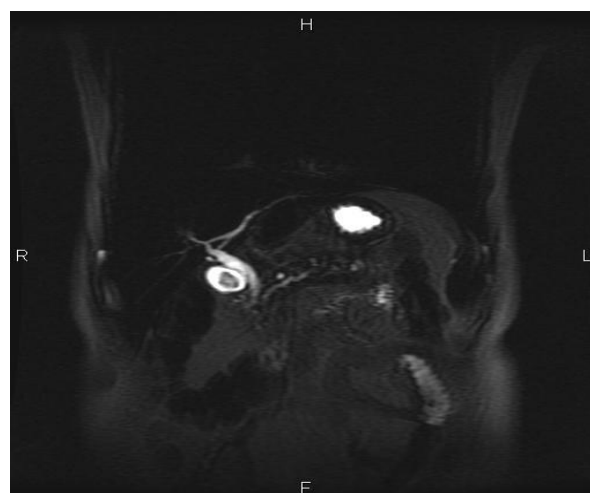
- “ 1) the presence of pancreatic exocrine insufficiency,
- 2) evidence of pathological pancreatic imaging,
- 3) the absence of type 1 diabetes mellitus (T1DM)-associated autoantibodies ” (11).

## Case Reports

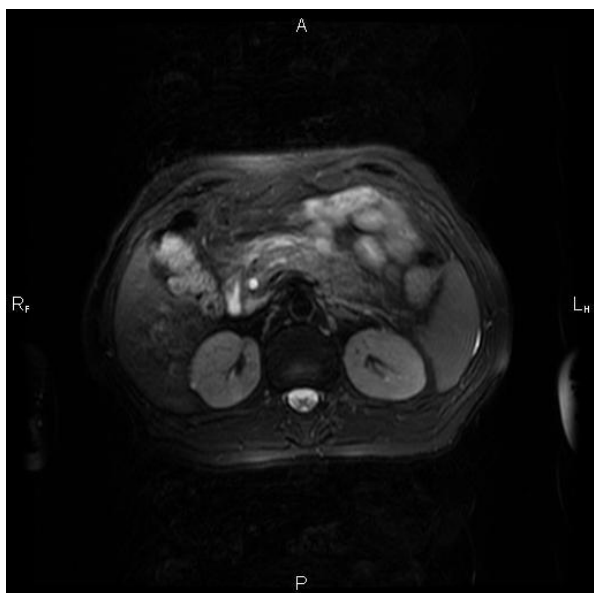
A 52-year old Caucasian man was diagnosed with chronic recurrent pancreatitis in 2007. The diagnosis was based on personal pathological history (repeated episodes of acute pancreatitis, biochemical, and imagistic investigations). A suggestive aspect of chronic pancreatitis evidenced by cholangio nuclear magnetic resonance is shown in Figures 1, 2, 3.



**Figure 1.** Axial T1 fat-suppressed section: pancreas with mild enhancement, with discrete estomption of physiological peripheral lobulation associated with peripancreatic fat stranding and right dilatation of the Wirsung duct



**Figure 2.** Coronal T2 single shot long TE section: irregular Wirsung duct dilatation associated with small peripheral canal dilations



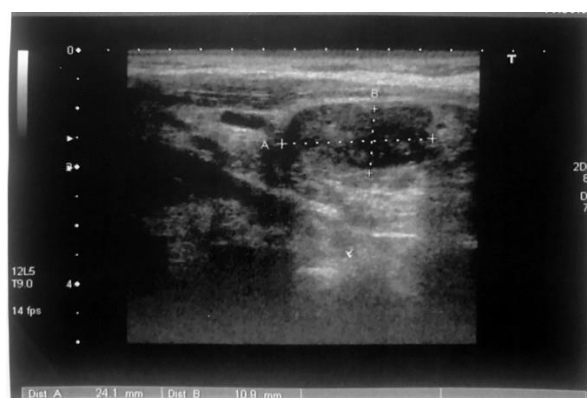
**Figure 3.** Axial T2 weighted fat saturated section: pericephalic pancreatic fat stranding with fine fluid associated collections.

The first episode of acute pancreatitis occurred in 2002 when the patient was hospitalized in an emergency department with intense pain in the epigastrium with dorsal irradiation after a high-fat meal. Upon admission, the patient had elevated values of serum amylase (817 U/l; normal range: < 100 U/l) and leukocytosis. The abdominal ultrasound revealed a slightly enlarged pancreas, non-homogeneous echotexture, and the absence of intra or extra pancreatic collections. The evolution was favorable under conservative treatment, with symptomatic remission and normalization of serum amylase levels. In October 2004, the patient returned to the emergency department with the same symptomatology. Paraclinical investigations revealed leukocytosis, serum amylase values of 1.300 U/l, and fluid in the peritoneal cavity without visible collections. Conservative treatment (antispasmodics, antisecretory drugs, anti-enzymatic drugs, antibiotics) led to improvement of the clinical symptomatology. In November 2004, an endoscopic retrograde cholangiopancreatography was performed, which established the diagnosis of stenotic papillomatosis. Papillosfincterectomy was performed with a stent mount that was removed one month later. In 2005, the patient underwent a surgical intervention for chronic lithiasis, and cholecystectomy was performed. In 2007, the patient presented 3 episodes of acute pancreatitis. The imaging investigations (computerized tomography and nuclear magnetic resonance) highlighted the presence of multiple intraductal calculi, and for this reason the extraction of calculi was performed with papillotomy and stenting (which had to be

changed every 6 months). Additional investigations on the etiology of recurrent chronic pancreatitis, initially diagnosed as idiopathic, revealed elevated values of total serum calcium (2.90 mmol/l, 2.99 mmol/l; normal range: 2.10-2.65 mmol/l) and serum parathormone (448.8 pg/ml; normal range 15.0-68.3 pg/dl). The presence of a parathyroid adenoma in the right lower pole of the thyroid was subsequently highlighted through ultrasound (Figure 4 and 5) and subsequently by scintigraphy. In September 2007, a parathyroidectomy was performed. In February 2008, the imaging control and the laboratory tests (after surgery) were performed. The values of total serum calcium were 2.49 mmol/l, serum parathormone 112 pg/ml, and thyroid scintigraphy (after the intravenous administration of 74 Mega-Becquerel Technetium 99 m) highlighted the homogenous distribution of the radioactive tracer without hot or cold areas. After parathyroidectomy, the patient showed a favorable evolution with the remission of the acute episodes of pancreatitis. The patient did not have any family history of diabetes. However, in 2017, he was diagnosed with diabetes. From the personal pathological history, the patient has been diagnosed with renal bilateral lithiasis with repeated eliminations of calculi.



**Figure 4.** Inferior parathyroid adenoma located between the carotid-tracheal-cross section



**Figure 5.** Inferior parathyroid adenoma located between the carotid-tracheal-longitudinal section

## Discussions

The relationship between primary hyperparathyroidism and recurrent nephrolithiasis is well known. The prevalence of renal lithiasis has dropped from 60-80% in initial studies to 7-20% in the more recent studies (12, 13, 14). The etiology of nephrolithiasis is multifactorial and involves genetic factors, hypercalciuria (a characteristic of hyperparathyroidism), hyperoxaluria, and cystinuria (15). In 2018, Letavernier and Daudon mention that hypercalciuria promotes the formation of kidney stones and the most common type of nephrolithiasis is calcium oxalate formed at Randall's plaques (16).

According to the American Gastroenterological Association Institute Guideline of Initial Management of Acute Pancreatitis, acute pancreatitis is defined as "an inflammatory condition of the pancreas that can cause local injury, systemic inflammatory response syndrome, and organ failure" (17). The etiology of acute pancreatitis includes obstructive causes, metabolic abnormalities, ischemia, and autoimmune diseases. In 10% of cases, the cause cannot be identified and the condition is defined as idiopathic pancreatitis (18).

The relationship between primary hyperparathyroidism and acute or chronic recurrent pancreatitis is not fully elucidated. Previous studies have highlighted that hypercalcemia, which is characteristic to hyperparathyroidism, can induce pancreatic injuries (19, 20, 21). There have been several hypotheses implicating hypercalcemia in the development of pancreatitis:

1. a greater extracellular amount of calcium generates the elevation of cytosolic calcium, which activates calcineurin and generates the zymogen activation and its transformation into trypsin (22, 23, 24). The intracellular zymogen activation is one of the earliest events for the initiation of acute pancreatitis and the development of chronic pancreatitis. Experimental studies mention that intracellular trypsin activity generates the apoptosis of the acinar cell (25, 26, 27);

2. high cytosolic calcium can generate the activation of nuclear factor Kappa-B (NF-kB) leading to local and systemic inflammation (28, 29);

3. calcium precipitations generate the formation of intraductal stones in the ducts (30).

Diabetes is associated with pancreatic disorders such as ductal pancreatic adenocarcinoma, hemochromatosis, pancreatitis, cystic fibrosis, and pancreatic surgery, but also with the alteration of bone quality (31). The prevalence of diabetes in association with pancreatitis was estimated, according to different studies, at 25-80% (32).

In a study by Pan and al. in 2016 in which 2011 patients with chronic pancreatitis were enrolled (1396 men and 615 women), the authors concluded that men are at higher risk of diabetes among patients with pancreatitis than women (hazard ratio, 1.51; 95% confidence interval, 1.28–2.33,  $p < 0.001$ ) (33). In chronic pancreatitis, the median age of the onset of diabetes mellitus is between 10-25 years (34). The consensus statement of PancreasFest 2012 recommended an annual screening for diabetes in patients with chronic pancreatitis by determining the fasting glucose and hemoglobin A1c; the impairment of these constants requires further investigations (35).

## Conclusions

In cases of recurrent renal lithiasis or pancreatitis, screening for hyperparathyroidism is recommended. Metabolic evaluation is required in patients with recurrent pancreatitis because of their high risk of developing diabetes.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

## References

1. Madkhali T, Alhefdhi A, Chen H, Elfenbein D. Primary hyperparathyroidism. *Ulus Cerrahi Derg.* 2016; 32(1): 58–66.
2. Lombardi G, Di Somma C, Rubino M, Faggiano A, Vuolo L, Guerra E, Contaldi P, Savastano S, Colao A. The roles of parathyroid hormone in bone remodeling: prospects for novel therapeutics. *Endocrinol Invest.* 2011; 34(7): 18-22.
3. Costanzo LS. Regulation of calcium and phosphate homeostasis. *Adv Physiol Edu.* 1998; 20(1): 206-216.
4. Bilezikian JP, Cusano NE, Khan AA, Liu LM, Marcocci C, Bandeira F. Primary hyperparathyroidism. *Nat Rev Dis Primers.* 2016; 2: 16033. DOI: 10.1038/nrdp.2016.33, 2016.
5. Silverberg SJ, Walker MD, Bilezikian JP. Asymptomatic Primary Hyperparathyroidism. *J Clin Densitom.* 2013; 16(1): 14-21.

6. Cope O, Culver PJ, Mixter Jr CG, Nardi GL. Pancreatitis, a diagnostic clue to hyperparathyroidism. *Ann Surg.* 1957; 145: 857–863.
7. Sitges-Serra A, Alonso M, de Lecea C, Gores PF, Sutherland DE. Pancreatitis and hyperparathyroidism. *Br J Surg.* 1988; 75: 158–160.
8. Khoo TK, Vege SS, Abu-Lebdeh HS, Ryu E, Nadeem S, Wermers RA. Acute Pancreatitis in Primary Hyperparathyroidism: A Population-Based Study. *J Clin Endocrinol Metab.* 2009; 94(6): 2115–2118.
9. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology.* 2011; 11(3): 279–294.
10. Makuc J. Management of pancreatogenic diabetes: challenges and solutions. *Diabetes Metab Syndr Obes.* 2016; 9: 311–315.
11. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c) - are we neglecting an important disease? *Eur J Intern Med.* 2013; 24(3): 203–206.
12. Mallette LE, Bilezikian JP, Heath DA, Aurbach GD. Primary hyperparathyroidism: clinical and biochemical features. *Medicine (Baltimore).* 1974; 53: 127–146.
13. Mollerup CL, Vestergaard P, Frøkjær VG, Mosekilde L, Christiansen P, Blichert-Toft M. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ.* 2002; 325(7368): 785–786.
14. Starup-Linde J, Waldhauer E, Rolighed L, Mosekilde L, Vestergaard P. Renal stones and calcifications in patients with primary hyperparathyroidism: associations with biochemical variables. *Ear J Endocrinol.* 2012; 166(6): 1093–1100.
15. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. *Pediatr Nephrol.* 2010; 25(5): 831–841.
16. Letavernier E, Daudon M. Vitamin D, Hypercalciuria and Kidney Stones. *Nutrients.* 2018; 10(3): 366.
17. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN. American Gastroenterological Association Institute Guideline of Initial Management of Acute Pancreatitis. *Gastroenterology.* 2018; 154(4): 1096–1101.
18. Sakorafas GH, Tsiotou AG. Etiology and pathogenesis of acute pancreatitis: current concepts. *J Clin Gastroenterol.* 2000; 30(4): 343–356.
19. Smith FB, Cook RT. Acute fatal hyperparathyroidism. *Lancet.* 1940; 2: 650.
20. Mixter CG, Keynes WM, Cope O. Further experience with pancreatitis as a diagnostic clue to hyperparathyroidism. *N Engl J Med.* 1962; 266: 265–272.
21. Sitges-Serra A, Alonso M, de Lecea C, Gores PF, Sutherland DE. Pancreatitis and hyperparathyroidism. *Br J Surg.* 1988; 75(2): 158–160.
22. Bai HX, Giefer M, Patel M, Orbi AI, Husain SZ. The Association of primary Hyperparathyroidism with Pancreatitis. *J Clin Gastroenterol.* 2012; 46(8): 656–661.
23. Sutton R, Criddle D, Raraty MG, Tepikin A, Neoptolemos JP, Petersen OH. Signal transduction, calcium and acute pancreatitis. *Pancreatology.* 2003; 3(6): 497–505.
24. Husain SZ, Grant WM, Gorelick FS, Nathanson MH, Shah AU. Caerulein-induced intracellular pancreatic zymogen activation is dependent on calcineurin. *Am J Physiol Gastrointest Liver Physiol.* 2007; 292(6): 1594–1599.
25. Ji B, Gaiser S, Chen X, Ernst SA, Logsdon CD. Intracellular trypsin induces pancreatic acinar cell death but not NF-kappaB activation. *J Biol Chem.* 2009; 284(26): 17488–98.
26. Dawra R, Sah RP, Dudeja V, Rishi L, Saluja AK. Intracinar trypsinogen activation is required for early pancreatic injury but not for inflammation during acute pancreatitis. *Gastroenterology.* 2011; 141(6): 2210–2217.
27. Stanescu AMA, Grajdeanu IV, Iancu MA, et al. Correlation of Oral Vitamin D Administration with the Severity of Psoriasis and the Presence of Metabolic Syndrome. *Revista de Chimie* 2018; 69(7): 1668–1672.
28. Chen X, Ji B, Han B, Ernst SA, Simeone D, Logsdon DC. NF-kappaB activation in pancreas induces pancreatic and systemic inflammatory response. *Gastroenterology.* 2002; 122(2): 448–457.
29. Baumann B, Wagner M, Aleksic T, von Wichert G, Weber CK, Adler G, Wirth T. Constitutive IKK2 activation in acinar cells is sufficient to induce pancreatitis in vivo. *J Clin Invest.* 2007; 117(6): 1502–1513.
30. Guy O, Robles-Diaz G, Adrich Z, Sahel J, Salrles H. Protein content of precipitates present in pancreatic juice of alcoholic subjects and patients with chronic calcifying pancreatitis. *Gastroenterology.* 1983; 84(1): 102–107.
31. Dănculescu Miulescu R, Guja L, Ochiana LC, Ungurianu A, Șeremet OC, Ștefănescu E. Serum markers of bone fragility in type-2 diabetes mellitus. *J Mind Med Sci.* 2019; 6(1): 78–85.

32. Hart PA, Bellin MD, Anderson DA, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC, Pandol SJ, Yadav D, Chari ST. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2016; 1(3): 226-237.
33. Pan J, Xin L, Wang D, Liao Z, Lin JH, Li BR, Du TT, Te B, Zou WB, Chen H, Ji JT, Zhong ZH, Hu LH, Li ZS. Risk Factors for Diabetes Mellitus in Chronic Pancreatitis. A Cohort of 2011 Patients. *Medicine (Baltimore)*. 2016; 95(14): e3251.
34. Malka D, Hammel P, Sauvanet A, Rufat P, O'Toole D, Bardet P, Belghiti J, Bemades P, Ruszniewski P, Lévy P. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology*. 2000; 119(5): 1324-1332.
35. Rickels MR, Bellin M, Toledo FGS, Robertson RP, Andersen DK, Chari ST, Brad R, Frulloni L, Anderson MA, Whitcomb DC. Detection, Evaluation and Treatment of Diabetes Mellitus in Chronic Pancreatitis: Recommendations from Pancreas Fest 2012. *Pancreatology* 2013; 13(4): 336-342.