Clinical aspects of pancreatogenic diabetes secondary to hereditary pancreatitis

Marcio Garrison Dytz1,2,3,4*, Pedro Arthur Hamamoto Marcelino3, Olga de Castro Santos1, Lenita Zajdenverg3, Flavia Lucia Conceição1, Tânia Maria Ortiga-Carvalho2 and Melanie Rodacki3

Abstract
Background: Hereditary pancreatitis is a rare inherited form of pancreatitis, characterized by recurrent episodes of acute pancreatitis with early onset and/or chronic pancreatitis, and presenting brittle diabetes, composed of episodes of nonketotic hyperglycemia and severe hypoglycemia. The existing literature regarding this form of diabetes is scarce. In this report, clinical features of pancreatogenic diabetes secondary to hereditary pancreatitis are presented along with recommendations for appropriate medical treatment.

Results: Clinical data from five patients of a family with pancreatogenic diabetes secondary to hereditary pancreatitis were analyzed. The average time between hereditary pancreatitis and diabetes diagnosis was 80 ± 24 months (range: 60–180 months) with a mean age of 25.6 ± 14.7 years (range: 8–42 years), four patients used antidiabetic agents for 46 ± 45 months and all progressed to insulin therapy with a mean dose of 0.71 ± 0.63 IU/kg (range: 0.3–1.76 IU/kg). The glycemic control had a high variability with average capillary blood glucose of 217.00 ± 69.44 mg/dl (range: 145–306 mg/dl) and the average HbA1c was 9.9 ± 1.9% (range: 7.6–11.6%). No ketoacidosis episodes occurred and there were several episodes of hospitalization for severe hypoglycemia.

Conclusions: Diabetes mellitus secondary to hereditary pancreatitis presents with early onset, diverse clinical presentation and with extremely labile glycemic control. Diabetes treatment varies according to the presentation and insulin is frequently necessary for glycemic control.

Keywords: Hereditary pancreatitis, Cationic trypsinogen, Pancreatogenic diabetes, Beta-cell

Background
Hereditary pancreatitis (HP) is a rare autosomal dominant disease characterized by recurrent episodes of acute pancreatitis that leads to permanent chronic pancreatitis. Common clinical manifestations are: abdominal pain, disabsorptive syndrome, diabetes mellitus (DM) and pancreatic cancer [1].

Pancreatic inflammation results in destruction of pancreatic islet with loss of β-cells (insulin), α-cells (glucagon), δ-cells (somatostatin) and PP-cells (pancreatic-polypeptide) [2] that can lead to the development of brittle diabetes, which is characterized by extreme blood glucose levels fluctuations, causing hyperglycemia or hypoglycemia [3]. This article focuses on clinical features and treatment of pancreatogenic diabetes secondary to HP.

Methods
Clinical data from a family with confirmed molecular diagnosis of HP was evaluated. A retrospective analysis of their medical records assessed weight, age, DM duration, interval between the diagnosis of HP and DM, use and dose of insulin, use of oral antidiabetic medications, HbA1c values, episodes of severe hypoglycemia, hospitalization for ketoacidosis and presence of chronic complications of DM. Download of data obtained through thirty days of self-monitoring of blood glucose using the Accu-Check Smart Pix Software®, was performed in order to measure and calculate average and standard deviation of blood glucose levels.
deviation (SD) of capillary blood glucose (CBG). The mutation screening has been previously described [4].

The local ethics committee approved the study protocol (169 11-CEP), in accordance with institutional ethical standards and national research committee. Patient informed consent form was obtained before initiating the study.

**Results**

The study evaluated five patients from a family with HP secondary to N29T mutation in exon 2 of the *PRSS1* gene (Fig. 1) [4]. In 3 patients, the HP diagnosis preceded DM, while in 2 the opposite occurred. The average time between HP and DM diagnosis was 80 ± 24 months (range: 60–180 months) (Table 1).

All patients used insulin. The mean dose was 0.71 ± 0.63 IU/kg (range: 0.27–1.76 IU/kg). In 4 patients, other drugs (Metformin and Glyburide) were used before insulin therapy was started, mean time of 46 ± 45 months (range: 4–96 months).

The average CBG was 217.00 ± 69.44 mg/dl (range: 145–306 mg/dl) with SD of 104.75 ± 15.56 mg/dl (range: 94–127 mg/dl). There was a high variability of CBG in all cases, with frequent hypoglycemic events and hyperglycemic excursions. HbA1c levels demonstrated the heterogeneity between patients, but most patients showed elevated levels (Fig. 2).

The average diabetes duration was 120.80 ± 80.32 months (range: 24–228 months). No ketoacidosis episodes occurred, although there were

---

**Table 1** Clinical features of pancreatogenic diabetes in affected patients

| Patient | Age of onset (years) | Duration of pancreatitis (years) | Duration of diabetes (years) | BMI (kg/m²) | Mean CBG/SD | Insulin dose (IU/kg) | HbA1c (mean) (%) | Chronic diabetes complications |
|---------|----------------------|---------------------------------|-------------------------------|-------------|-------------|----------------------|----------------|--------------------------------|
| 1       | 8                    | 53                              | 19                            | 25.4        | 184/94      | 0.3                  | 7.6            | No                            |
| 2       | 5                    | 36                              | 13                            | 21.7        | 233/104.4   | 0.83                 | 11.6           | Retinopathy                   |
| 3       | 14                   | 25                              | 2                             | 29.7        | –           | 0.27                 | 8.2            | No                            |
| 4       | 2                    | 16                              | 10                            | 22.6        | 145/94.8    | 0.41                 | 11.5           | No                            |
| 5       | 4                    | 12                              | 5                             | 22.7        | 306/127.5   | 1.76                 | 10.9           | Neuropathy                    |

*BMI* body mass index, CBG capillary blood glucose, SD standard deviation

* Mean of 5 years, method high-performance liquid chromatography (HPLC)
episodes of hospitalization because of severe hypoglycemia. Surgical procedures were performed on patients 4 and 5, respectively, for refractory pain and abdominal complication. Patients 2 and 5 presented microvascular lesions secondary to diabetes with nonproliferative diabetic retinopathy with macular edema and distal symmetrical sensorimotor polyneuropathy accompanied by autonomic neuropathy, respectively.

**Discussion**

In this study, we describe the glycemic pattern of five patients with diabetes secondary to a mutation in the *PRSS1* gene, which leads to an increased autocatalytic conversion of trypsinogen to active trypsin, that results in autodigestion and damage to the acinar cells [5, 6].

Mutations in the *PRSS1* gene (R122H, N29I, A16V, and other less prevalent) are responsible for greater than 70%
of mutations in HP kindreds [7, 8], but other mutations have also been described (Fig. 3) [9–11].

A high rate of hypoglycemia and CBG variability was observed in these patients with diabetes secondary to HP. The marked glycemic lability is probably due not only to a continued loss of insulin secreting β-cells but also from counter regulatory glucagon secreting α-cells. Additionally, nutrients malabsorption resulted in impaired incretin secretion and thereby diminished insulin release. Moreover, the lack of other paracrine or endocrine factors secreted by the pancreatic cells may also contribute to this glycemic pattern [12].

Unlike type 1 DM, even with high glucose levels no patient developed ketoacidosis. The reasons that may warrant this is that the β-cell deficit is seldom absolute and it occurs concomitantly with the loss of α-cells [13]. All patients required insulin therapy, but the progression of the pancreatic endocrine failure was extremely variable. In some of the cases, insulin was necessary shortly after the diabetes diagnosis, while in others, oral drug therapy without insulin was possible for years.

Oral antidiabetic agents may be appropriate in early pancreatogenic diabetes (HbA1c < 8.0%). Metformin should be the drug of first choice, in the absence of contraindications, especially if concomitant insulin resistance is evidenced, and if it is tolerated due to common gastrointestinal adverse effects and weight loss [14]. Besides that, it is possible that Metformin might reduce the risk of pancreatic cancer, and therefore would have a theoretical rationale in chronic pancreatitis [15]. Oral therapy with insulin secretagogues (sulfonylurea and glinides) may also be considered as second-line therapy, but should be

---

**Fig. 3** Schematic mechanism underlying mutations-associated pancreatitis. The PRSS1 (Cationic Trypsinogen) mutation leads to a gain-of-function with an increased conversion of intrapancreatic trypsinogen to trypsin. The SPINK1 (Serine Protease Inhibitor Kazal type 1) and CTRC (Chymotrypsin C) mutations lead to loss of defenses against the activation of trypsinogen. Mutations in CPA1 (carboxypeptidase A1) generate misfolded proteins leading to endoplasmic reticulum stress.
aware of hypoglycemia in patients with inconsistent meal ingestion [3]. Thiiazolidinediones, incretin based therapies and SGLT2 inhibitors should be avoided because of side effects and lack of data in this context [3, 16].

In advanced pancreaticogenic diabetes, insulin therapy is the preferred treatment, and especially during acute episodes of pancreatitis or hospitalized patients, and severe malnutrition patients in which the anabolic effects of insulin are desired. Patients should be treated using general insulin dosing and regimen guidelines for type 1 diabetes [3, 16]. The patients studied used NPH and regular insulin because it is the first choice in the local healthcare public system. Despite the use of human insulin, glycemic control was more unpredictable than expected with high glycemic variability. The insulin analogues or insulin pump therapy are treatment options that may allow a more stable glycemic control.

Moreover, the islet autotransplant might be an option for patients with severe chronic pancreatitis, who have debilitating abdominal pain refractory to medical or endoscopic interventions and for which total pancreatectomy is indicated [17, 18]. Patient 4 underwent pancreatectomy and could have benefited from this therapy to preserve the function of the remaining β-cells.

In summary, these data indicate that DM secondary to HP presents clinical heterogeneity among patients, but with high glycemic variability and difficult management. Hence, molecular diagnosis should be performed in suspicious patients of HP because it allows the proper approach. Strategies to improve the glycemic control in affected patients should also be pursued.

Abbreviations
HP: hereditary pancreatitis; DM: diabetes mellitus; SD: standard deviation; CBG: capillary blood glucose; NN: no mutation; NM: heterozygous mutation; BMI: body mass index; HPLC: high-performance liquid chromatography; PRSS1: cationic trypsinogen; SPINK1: Serine Protease Inhibitor Kazal type 1; CTRC: Chymotrypsin C; CPA1: carboxypeptidase A1.

Authors’ contributions
MGD, FLC, TMOC and MR participated in the design of the study; MGD, PAHM and OCS collected patient data; MGD, LZ, TMOC and MR analyzed data; and MGD, FLC, TMOC and MR participated in the design of the study; MGD, PAHM and OCS collected patient data; MGD, LZ, TMOC and MR analyzed data; and MGD, FLC, TMOC and MR participated in the design of the study; MGD, PAHM and OCS collected patient data; MGD, LZ, TMOC and MR analyzed data; and MGD, FLC, TMOC and MR participated in the design of the study.

Authors details
1 Endocrinology Section, Department of Internal Medicine, Medical School, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil. 2 Laboratory of Translational Endocrinology, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil. 3 Diabetes and Nutrology Section, Department of Internal Medicine, Medical School, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil. 4 Endocrinology Section, Hospital Universitário Clementino Fraga Filho, Rua Rodolfo Paulo Rocco 255, Ilha do Fundão, Rio de Janeiro, RJ 21941-913, Brazil.

Acknowledgements
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
All data generated or analysed during this study are included in this published article and in the article [4].

Consent for publication
All patients signed a consent form, in which they agree with the publication of the results of the study.

Ethics approval and consent to participate
The ethics committee of Federal University of Rio de Janeiro approved the study protocol (169 11-CEP) on April 24th, 2012, in accordance with institutional ethical standards (Declaration of Helsinki) and national research committee. Patient informed consent form was obtained before initiating the study.

Funding
This work was supported by the FAPERJ (Foundation for Research Support of the State of Rio de Janeiro) and the CNPq (National Council for Scientific and Technological Development).

Received: 23 April 2016 Accepted: 7 January 2017
Published online: 13 January 2017

References
1. Rebours V, Lévy P, Ruszniewski P. An overview of hereditary pancreatitis. Dig Liver Dis. 2012;44(1):8–15.
2. Weir GC, Bonner-Weir S. Islets of Langerhans: the puzzle of intras‑let interactions and their relevance to diabetes. J Clin Invest. 1990;85(4):983–7.
3. Rickels MR, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. Pancreatology. 2013;13(4):336–42.
4. Dytz MG, Mendes de Melo J, de Castro Santos O, da Silva Santos ID, Rodacki M, Conceição FL, et al. Hereditary Pancreatitis Associated with the N29T mutation of the PRSS1 gene in a Brazilian family: a case‑control study. Medicine (Baltimore). 2015;94(37):e1508.
5. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet. 1996;14(2):141–5.
6. Sahin‑Toth M, Toth M. Gain‑of‑function mutations associated with hereditary pancreatitis enhance autoactivation of human cationic trypsinogen. Biochem Biophys Res Commun. 2000;278(2):286–9.
7. Howes N, Lerch MM, Greenhalh W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. 2004;2(3):252–61.
8. Rebours V, Boutron‑Rautuc MC, Schnee M, Fèrec C, Le Maréchal C, Hentic O, et al. The natural history of hereditary pancreatitis: a national series. Gut. 2009;58(1):97–103.
9. Aoun E, Chang CC, Greer JB, Papachristou GI, Barmada MM, Whitcomb DC. Pathways to injury in chronic pancreatitis: decoding the role of the high‑risk SPINK1 N34S haplotype using meta‑analysis. PLoS ONE. 2008;3(4):e2003.
10. Rosenthal J, Witt H, Szmol R, Bhata E, Oszvári B, Landt O, et al. Chymotrypsin C (CTRC) variants that diminish appearance or secretion are associated with chronic pancreatitis. Nat Genet. 2008;40(1):78–82.
11. Witt H, Beer S, Rosenthal J, Chen JM, Chandak GR, Masamune A, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat Genet. 2013;45(10):1216–20.
12. Hardt PD, Bendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care. 2008;31(Suppl 2):S165–9.
13. Sjoberg RJ, Kidd GS. Pancreatic diabetes mellitus. Diabetes Care. 1989;12(10):715–24.
14. Association A.D. (7) Approaches to glycemic treatment. Diabetes Care. 2015;38(Suppl):S41–8.
15. Sadeghi N, Abbruzzese JL, Yeung SC, Hassan M, Li D. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin Cancer Res. 2012;18(10):2905–12.
16. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World J Gastroenterol. 2013;19(42):7276–81.
17. Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. Pancreatology. 2014;14(1):27–35.
18. Kesseli SJ, Smith KA, Gardner TB. Total pancreatectomy with islet autologous transplantation: the cure for chronic pancreatitis? Clin Transl Gastroenterol. 2015;6:e73.