Current Diabetes Reports (2020) 20:16
https://doi.org/10.1007/s11892-020-01299-8

OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (JJ NOLAN AND H THABIT, SECTION EDITORS)

Diabetes of the Exocrine Pancreas Related to Hereditary Pancreatitis, an Update

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Abstract

Purpose of Review The aim was to review evidence about diabetes secondary to hereditary pancreatitis, seeking novel diagnostic and treatment features.

Recent Findings Hereditary pancreatitis (HP) is an autosomal dominant condition, characterized by recurrent episodes of acute pancreatitis, progression to fibrosis, and chronic pancreatitis. Clinical presentation includes diabetes of the exocrine pancreas (DEP). HP prevalence ranges from 0.3 to 0.57 per 100,000 people, with up to 80% of these develop DEP. This condition often requires specific interventions: with regard to metabolic control, metformin is the first choice for those with mild DEP, and for those in advanced disease, insulin is considered the first-line therapy. Insulin analogues and insulin pump therapy are preferred due to the brittle glycemic pattern and risk of hypoglycemia. In case of exocrine insufficiency, pancreatic enzyme replacement therapy is recommended. Pancreatic polypeptide administration is a promising novel treatment feature.

Summary DEP due to HP appears to be a misdiagnosed condition. The requirement of specific management demonstrates the importance of this matter; therefore, appropriate recognition and classification are important.

Keywords Hereditary pancreatitis · Diabetes of the exocrine pancreas · Brittle diabetes · PRSS1 · SPINK1

Introduction

Hereditary pancreatitis (HP) is an autosomal dominant condition, with an estimated penetrance of 80%. It is a rare disease characterized by recurrent episodes of acute pancreatitis, progression to fibrosis, and chronic pancreatitis (CP) [1••]. The first HP report was in 1952 by Comfort and Steinberg, who suggested a genetic background [2].

It was only in 1996 that an associated genetic mutation, R122H, was identified by Whitcomb et al. in the cationic trypsinogen gene (PRSS1) [3]. In the following years, several PRSS1 mutations and diverse HP related genes were discovered, specifically the serine protease inhibitor Kazal type 1 (SPINK1), the cystic fibrosis transmembrane conductance regulator (CFTR), the chymotrypsin C (CTRC) [4–7], and the carboboxypeptidase A1 (CPA1) [4, 8].

The clinical presentation of HP includes abdominal pain, malabsorptive syndrome due to pancreatic exocrine dysfunction, and diabetes mellitus (DM) due to islet cell damage [9]. Diabetes mellitus caused by exocrine insufficiency used to be called by pancreatogenic DM or type 3c diabetes (T3cDM) [10] notwithstanding more recently the medical literature refers to it as diabetes of the exocrine pancreas (DEP) [11]. DEP encompasses diverse causes with CP the most common, although pancreatic ductal adenocarcinoma and cystic fibrosis are equally of importance [12].

Diabetes is an independent risk factor of mortality in these patients, with micro and macrovascular damage caused by DEP being a significant late sequelae of CP [13]. While the prevalence of DM is estimated to be 9.3% in the US general

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Published online: 28 March 2020

population [14], in CP patients it is up to about 80% [14, 15], which demonstrates the importance of this matter.

Therefore, this article aims to review the literature on DEP and its relationship to hereditary pancreatitis.

Epidemiology

There is currently insufficient data to precisely estimate the prevalence of DEP due to HP [15, 16]. In addition to the small number of studies performed in this condition, DEP is also underestimated and underdiagnosed, making estimation of worldwide prevalence challenging [17].

Chronic pancreatitis is a major cause of DEP (25–80%) [18••, 19] with an incidence of 9.62 cases per 100,000 person-years [20]. Due to the difficulty in diagnosing CP, the prevalence of CP has been conservatively estimated to be as high as 120–143 per 100,000 individuals [21]. Adopting cohorts with diabetes to estimate DEP prevalence, it is acceptable to assume that this ranges from 5 to 10% in a population of individuals with diabetes [12]. Moreover, HP is an underestimated cause of CP, with up to 32% of idiopathic chronic pancreatitis having underlying genetic mutations [22]. HP has an estimated prevalence that varies greatly depending on the region, between 0.3 to 0.57 per 100,000 according to national cohort data [22, 23].

Analyzing several HP regional studies, there are significant variation in epidemiological data. The discrepancy is more notable in PRSS1 mutation percentage, which ranges from 10.5 to 67.5, and is directly influenced by the different clinical criteria used to determine genetic testing. The lack of a uniform diagnostic criteria leads to heterogeneous samples and may also explain discordant diabetes rates, median time to DEP, and cumulative risk of DM found in these series (Table 1).

Genetics

Since 1996, when the first genetic association was described, more than 35 mutations of PRSS1 were discovered [30, 31]. This autosomal-dominant gene mutation pattern, found in 65–100% of hereditary pancreatitis kindreds [16], is associated with an increase of autocatalytic conversion of trypsinogen to active trypsin (Fig. 1) [32]. This abnormal intrapancreatic process is responsible for the progressive destruction of acinar cells, resulting in ductal and interstitial injury [4]. The most common PRSS1 mutations (R122H and N29I) are those associated with gain of function, responsible for enhancing trypsinogen autoactivation, and increasing trypsin stability [33, 34].

In contrast, SPINK1 is responsible for controlling intra pancreatic trypsin 1 activity, revealing itself as the first line of defense against this abnormal conversion. It represents a loss of function mutation with a recessive inheritance pattern that results in a decreased trypsin degradation [35]. Facing SPINK1's inheritance model, in which less than 1% of the carriers develop CP, it was proposed a complex pathophysiology participation of gene-environment and gene-gene interactions [36]. These genetic mutations build a high-risk model that might help explain disparate CP susceptibilities in alcoholic and tropical pancreatitis diseases [36, 37].

Other genetic defects are also involved, such as CTRC, which is responsible for all human trypsin and trypsinogen degradation [38], yet CTRC mutation appears to be a low-risk factor [6]. In other hand, CFTR may cause cystic fibrosis in severe mutation cases [39]; it is also a loss function gene, reducing bicarbonate conductance [40]. A number of distinct genes have recently been related to HP: CPA1 due to endoplasmic reticulum stress [41], CTSB due to a suppositional premature trypsin activation [42], and CLDN2 and CASR which pathological implications are currently unknown [43, 44].

Table 1 Epidemiological and clinical data based on HP regional series

Author/year of publication	Region	No. of patients	HP prevalence/ 100,000	PRSS1 Mutation (%)	Diabetes (%)	Median time to DEP (years)	Cumulative risk of DM at 50 years (%)
Applebaum-Shapiro et al/2001 [24]	USA	717	–	67	–	–	–
Keim et al/2001 [25]	Germany	550	–	18.4	24	–	–
Howes et al/2004* [1]	Europe	527	–	81	32	53	47.6
Masamune et al/2017 [26]	Japan	271	0.35	41	21.6	58	36
Rebours et al/2008 [23]	France	200	0.3	67.5	26	38	–
Joergensen et al/2010 [22]	Denmark	122	0.57	14.8	32	–	–
Räty et al/2007 [27]	Finland	36	–	22	0	–	–
Palaez-Luna et al/2014 [28]	Mexico	19	–	10.5	5	–	–
Dytz et al/2015 [29]	Brazil	16	–	62.5	31.3	–	–

*On behalf of the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC)

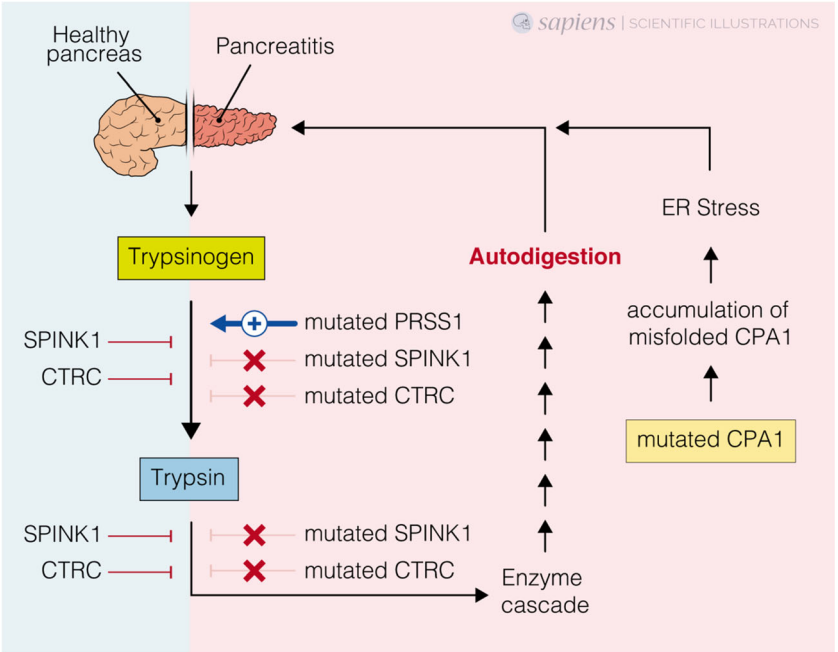

Fig. 1 Schematic mechanism underlying mutations associated with pancreatitis. ER, endoplasmic reticulum. Use authorized by Dytz et al., 2015 [29]

Pathophysiology

Chronic pancreatitis is marked by recurrent acute episodes inducing severe damage to the endocrine and exocrine parenchyma, which may lead to their respective pancreatic insufficiencies [45]. An inflammatory pattern is observed in all types of events which induce exocrine injuries, causing increased intracellular levels of activated pancreatic enzymes. In the long term, there is an ongoing damage to the pancreas via oxidative stress [46].

Exocrine insufficiency due to progression of inflammatory and fibrotic processes occurs in up to 37% of the patients with HP at 50 years of age [1••] and owing to the large pancreatic reserve available; pancreatic exocrine insufficiency only occurs when more than 90% of exocrine function is lost [47]. Malabsorptive syndrome is one of the most important HP's clinical repercussion, and it is also significantly associated with a higher mortality [48].

Endocrine insufficiency is observed in up to 47% of the patients with HP at 50 years and 79% at 80 years [1••]. Although continuous damage to the islet cells is parallel with the exocrine degradation, overt diabetes occurs later in DEP [49]. The DEP's pathology basis is endogenous insulin deficiency, due to initially an inflammatory environment and β-cells dysfunction, followed by significant β-cells loss caused by progressive fibrosis [50••].

Aside from β-cells loss, there is also fundamental α-cells dysfunction resulting in counter regulatory hormone deficiency. Lack of glucagon counter-regulatory response is a significant contributor to glycemic lability, and variability frequently observed in these patients [50••]. Lack of coordinated digestion and absorption, diminished paracrine, and endocrine factors as well as impaired activation of hepatic gluconeogenesis are other mechanisms also associated to the brittle diabetes glycemic patterns pathophysiology [17]. Hypoglycemic excursions in the context of increased glycemic variability is a major clinical endpoint of the aforementioned mechanisms and is an important risk factor of increased mortality [51••].

Deficiency of pancreatic polypeptide (PP) response may also play a key role in hepatic insulin resistance [52]. PP is a glucoregulatory hormone that regulates the expression of insulin receptors which modulate hepatic insulin sensitivity response [53]. Therefore, DEP appears to also be an independent risk factor contributing to increased peripheral insulin resistance and diabetes [54].

Clinical Aspects

HP is distinguished by an early age of onset; the primary manifestation is usually acute pancreatitis at 10–12 years [1••, 23], although in some studies the median age was even earlier [55, 56]. The evolution to exocrine insufficiency mostly occurs at second or third decade of life, when epigastric abdominal pain becomes the most common symptom, which might be followed by exocrine pancreatic insufficiency syndrome including abdominal cramps, fatty stools associated with steatorrhea, and malnutrition [57].

The overall median onset age of DEP due to HP is estimated to be 53 years [1••]; paradoxically, DEP can sometimes be the primary presentation of HP [58]. Its duration does not appear to be influenced by mutation status or gender [1••, 26]. Notwithstanding, DEP is generally reported as a brittle disease; there is a lack of data about rates of hypoglycemia in

DEP [18••, 58]. Available data suggest that episodic non-severe hypoglycemia occurs in up to 79% of patients with pancreatogenic diabetes, and severe hypoglycemia occurs in up to 41% [59]. The reported increased risk of hypoglycemia is associated with increased mortality [60].

There are also exiguous data about metabolic control in DEP especially due to HP [15]. A Brazilian cohort study demonstrated high rates of hypoglycemia and capillary blood glucose variability in patients with DM associated with HP [61]. Another study compared glycemic variability (GV) between DEP and T2DM, with higher GV and rates of hyperglycemia observed in the DEP group [62]. Even with high glucose levels, these patients rarely present ketoacidosis, probably because of the remaining β-cells function, in which absolute insulin deficiency is uncommon [63, 64].

Diagnosis

Diabetes mellitus in the context of disease of the exocrine pancreas is not commonly recognized by physicians; its diagnosis might be challenging, specially due to a lack of definitive criteria, what should be the explanation of the fact that the most cases are initially misdiagnosed as T2DM. Edwald and Bretzel propose the following criteria for DEP secondary to CP (Table 2) [18••]:

These criteria might be helpful, however, have been criticized for the laboriousness of applying them to all clinical settings [65]. For the American Diabetes Association (ADA) recommendations, there are no specific diagnostic criteria for DEP. Even though, the use of the above mentioned major criteria is encouraged by the association as a distinguishing feature [11].

The most commonly used criteria for HP was defined by European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) trial and is made on basis of two first-degree relatives, or three or more second-degree relatives, in two or more generations with recurrent acute pancreatitis and/or CP, for which there were no predisposing factors [1••]. Once HP diagnosis is made, diabetes (or prediabetes) screening might be performed annually with random glucose, HbA1c, and/or oral glucose tolerance test (OGTT) [50••, 58]. This investigation is crucial since it is observed a substantial increase in diabetes prevalence with longer duration of HP [66].

Despite the DEP diagnostic proposal criteria, in usual clinical practice, DM patients who present with malabsorptive syndrome associated to episodes of acute pancreatitis and a glycemic brittleness hard to control should raise clinical suspicions of DEP. A history of recurrent unexplained attacks of acute pancreatitis, unexplained chronic pancreatitis episode with or without a positive family history, as a well as CP episodes in children should instigate investigation for HP, mainly in DM patients. Thus, more studies are needed to define clinical and characteristic features with reasonable sensitivity and specificity for diagnosis of DEP related to HP.

Management

DEP often requires specific interventions [67]. As insulin deficiency is a key pathophysiological feature of DEP, insulin is considered first line therapy for most patients with advanced disease [68]. The initial dose calculation of insulin therapy should follow those on multiple daily injections (MDI) in T1DM [50••]. Despite of the side effects, such increasing risk of pancreatic cancer, with an odds ratio of 2.78 and hazard ratio of cancer-related mortality of 1.9 ($p < 0.05$) [69, 70], insulin remains the preferred treatment especially during acute episodes of pancreatitis as well in hospitalized and malnourished patients, in which the anabolic insulin effects are desired [50••].

Insulin therapy presents a risk of hypoglycemia notedly for those with an increased peripheral insulin sensitivity [71]. The labile glycemic control is the reason why glucose levels should be slightly upward the normal targets, as HbA1c < 7%, aiming to improve the quality of life [72, 73]. Providing DM structured education programs is important to achieve target glycemic control and to allow flexibility in dietary

Table 2 Diagnostic criteria for DEP secondary to CP

Major criteria (all must be present)
• A diagnosis of diabetes mellitus.
• Evidence of exocrine pancreatic insufficiency (according to the monoclonal fecal elastase-1 test or direct function tests).
• Pathological pancreatic imaging (endoscopic ultrasound, magnetic resonance imaging, or computed tomography).
• Absence of type 1 diabetes mellitus associated autoimmune markers.
Minor criteria
• Impaired beta cell function (e.g., HOMA-B, C-peptide/glucose-ratio).
• No excessive insulin resistance (e.g., HOMA-IR).
• Impaired incretin secretion (e.g.GLP-1, pancreatic polypeptide).
• Low serum levels of lipid soluble vitamins (A, D, E, and K).

intake [74]. These planned and graded process should facilitate the knowledge, skills, and ability for diabetes self-management by enhancing health-promoting behaviors and empower people with DM to implement flexible intensive insulin therapy [75].

Some treatment approaches may also be considered aiming to reduce the risk of hypoglycemia, such the insulin analogues and insulin pump therapy [50••, 61]. Recently, the use of the real-time continuous glucose monitoring (RT-CGM) for people with type 1 diabetes treated with MDI have been shown to be effective in improving glycemic control and reducing the risk of hypoglycemia [76]. RT-CGM might represent a change management approach for patients with problematic hypoglycemia, such DEP patients, since markedly improves HbA1C and glycemic variability indices, as well as reduces the number of hypoglycemic excursions. It is reasonable that RT-CGM benefits can be extended to DEP patients treated with MDI, representing high clinical relevance, especially for those who are unable to use insulin pumps [77].

Additional features may be held intending to improve the metabolic control of these patients. Coefficient of variation (CV), considered the main acceptable measure of glycemic variability, and standard deviation (SD) have been commonly used as glycemic variability indices. Both CV and SD are obtained using continuous glucose monitoring measures. These are robust features which use should improve glycemic control while avoiding hypoglycemia [78]. Their clinical application is supported by the fact that HbA1c is a poor predictor of hypoglycemic episodes, specially the silent ones, whereas low GV represents trustingly a low risk of severe hypoglycemia [79, 80].

In those with mild severity of DM (HbA1c < 8%), oral hypoglycemic agents might be considered [50••]. Metformin should be the first choice; besides of the convenience of using an oral agent, this drug offers a theoretical anti-neoplastic effect, decreasing the risk of pancreatic ductal adenocarcinoma [69, 81]. Nevertheless, it also causes weight loss and important gastrointestinal adverse effects that need to be tolerated [50••]. A second-line therapy is the thiazolidinediones (TZD); these drugs appear to improve the hepatic and peripheral insulin sensitivities in experimental studies [82]. However, TZD should only be recommended considering the possible impact of their side effects, especially the risk of fracture and congestive heart failure [83].

Incretin-based therapies, including glucagon-like peptide-1 (GLP-1) analogues and oral dipeptidyl peptidase-4 inhibitors, are not commonly recommended. Notwithstanding enhancing insulin secretion, these drugs are associated with a hypothetical increased risk of drug-induced pancreatitis and pancreatic cancer [84]. In the same way, sodium-glucose cotransporter 2 inhibitors (SGLT2) should be avoided due to the lack of data in this context, as well as the important side effects such risk of dehydration and weight loss [85].

The primary medical nutrition therapy goals should include preventing or treating malnutrition, controlling symptoms of steatorrhea, and minimizing meal induced hyperglycemia [50••]. In case of exocrine insufficiency of any degree to prescribe pancreatic enzyme replacement therapy (PERT) is recommended. This replacement aims to increase postprandial response, enable the absorption of vitamin D, and to prevent A, D, E, and K vitamins deficiency [86]. PERT and vitamin D replacement are critical to prevent metabolic bone disease and osteoporosis in these patients [87].

DEP glucose levels are usually reported as difficult to control. Facing this struggle, PP administration reveals itself as a promising novel feature. Several studies showed that PP therapy reversed the hepatic insulin resistance, enabled effective utilization of circulating insulin, and improved glycemic control, decreasing insulin requirements in DEP patients [52, 88–90]. Whether it is available, a semester screening of pancreatic polypeptide response might be helpful, if reduced would assist in early identification of impaired pancreatic endocrine function, and consequent increased risk of diabetes in HP patients with CP [91].

Moreover, total pancreatectomy with islet autotransplantation (TPIAT) might be an option in patients with severe complications, suffering refractory abdominal pain, or in those with high risk of pancreatic cancer. This endocrine function-preserving autologous islet cell isolation and re-implantation method cannot be considered a prevention nor a treatment for diabetes. The primary objective of this surgical approach is the pain relieving [51••]. Therefore, in selected patients, TPIAT has been shown to be effective in restoring the quality of life, as well as improving the glycemic control [92].

Complications

DM and CP are both independent risk factors for pancreatic ductal adenocarcinoma; therefore, there is no doubt that this combination, present in people with DEP, represents a significant increased risk of developing this type of cancer [93]. Moreover, it was estimated a 35% lifetime risk of developing pancreatic cancer for patients with HP notedly those bearing the R122H mutation [94]. Screening HP patients for pancreatic cancer has been advocated and should be performed with pancreatic magnetic resonance imaging and/or endoscopic ultrasound in experienced centers. This surveillance should be initiated at age [50] years or 10 years younger than the earliest age of pancreatic cancer in the family [95]. Furthermore, in HP symptomatic patients, genetic testing is justified aiming to clarify etiology and provide genetic counseling [16].

DEP appears to share a similar risk for the micro and macro-vascular complications observed in T1DM [66]. This risk is diminished by a good glycemic control. GV, higher in DEP than in type 2 diabetes, is considered an independent risk

for these complications [96]. Further studies are needed to endorse the association with higher rates of vascular complications. Therefore, these patients should be monitored following the same guidelines proposed for type 1 and 2 DM [50••].

Conclusion

In summary, this study contributes to the characterization of diabetes mellitus in the context of disease of the exocrine pancreas related to hereditary pancreatitis. Nevertheless, more surveys are required to establish practicable clinical diagnostic criteria, as the lack of this feature carries us into a mis- and underdiagnosing scenario. A clinical suspicion of DEP due to HP should instigate investigation, since the correct diagnosis allows an effective assistance of these patients, recommending precise and needed treatments as well as preventing severe complications. Furthermore, we believe that this article has high clinical relevance, seeing that reviews HP endocrine outcomes and detailing novel diagnostic and treatment features about the theme.

Author Contributions Both authors wrote the manuscript and contributed to the design, drafting, and reviewing the paper.

Funding Information No specific grant was received from any funding agency in the public, commercial, or not-for-profit sector for the publication of this report.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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