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Contents

ABOUT COVER

Dr. Koch has served as an Editor–in-Chief of the *World Journal of Diabetes* since May 2017, and since 2005 has been Professor of Medicine (Gastroenterology) at Georgetown University School of Medicine in Washington, DC, United States. Dr. Koch completed training in gastrointestinal physiology within the Department of Physiology and Biophysics as a Research Associate at Mayo Medical School in Rochester, Minnesota. Dr. Koch is an editorial board member on several medical journals, is a reviewer for multiple scientific and medical journals, and has published more than 150 original manuscripts, invited reviews, and book chapters. Dr. Koch's ongoing research interests include studies of the pathophysiology of obesity and post-bariatric surgical disorders, and studies of the benefits of endoscopic and bariatric surgical weight loss procedures in individuals with diabetes mellitus.

AIMS AND SCOPE

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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RESPONSIBLE EDITORS FOR THIS ISSUE

Islet cell dysfunction in patients with chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is characterized by progressive inflammation and fibrosis of the pancreas that eventually leads to pancreatic exocrine and endocrine insufficiency. Diabetes in the background of CP is very difficult to manage due to high glycemic variability and concomitant malabsorption. Progressive beta cell loss leading to insulin deficiency is the cardinal mechanism underlying diabetes development in CP. Alpha cell dysfunction leading to deranged glucagon secretion has been described in different studies using a variety of stimuli in CP. However, the emerging evidence is varied probably because of dependence on the study procedure, the study population as well as on the stage of the disease. The mechanism behind islet cell dysfunction in CP is multifactorial. The intra-islet alpha and beta cell regulation of each other is often lost. Moreover, secretion of the incretin hormones such as glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide is dysregulated. This significantly contributes to islet cell disturbances. Persistent and progressive inflammation with changes in the function of other cells such as islet delta cells and pancreatic polypeptide cells are also implicated in CP. In addition, the different surgical procedures performed in patients with CP and antihyperglycemic drugs used to treat diabetes associated with CP also affect islet cell function. Hence, different factors such as chronic inflammation, dysregulated incretin axis, surgical interventions and anti-diabetic drugs all affect islet cell function in patients with CP. Newer therapies targeting alpha cell function and beta cell regeneration would be useful in the management of pancreatic diabetes in the near future.

Key words: Alpha cell; Beta-cell; Chronic pancreatitis; Diabetes; Incretins; Pancreatic diabetes

Core tip: Chronic pancreatitis (CP) is a progressive inflammatory disorder leading to islet cell dysfunction and subsequent development of diabetes. The disease pathology is complex and is characterized by dysregulation of both the islet cells and the incretin axes. The different surgical procedures performed in patients with CP and antihyperglycemic drugs used to treat diabetes associated with CP also affect islet cell function. Diabetes secondary to CP is difficult to treat and contributes to disease morbidity. Newer therapies targeting alpha cell function and beta cell regeneration would be useful in the management of pancreatic diabetes in the near future.

INTRODUCTION

Chronic pancreatitis (CP) is a slow progressive inflammatory condition of the pancreas, resulting in pancreatic exocrine and endocrine insufficiency. Diabetes secondary to pancreatic pathology (acute pancreatitis, CP, and pancreatic adenocarcinoma) is termed type 3c diabetes[1]. Diabetes mellitus (DM) due to CP is characterized by predominant post-prandial hyperglycemia and fasting hyperglycemia usually occurs later. Hence, fasting glucose measurements alone can miss the diagnosis at an early stage of CP. It is often difficult to control blood glucose levels due to unpredictable swings between hyper and hypoglycemia, the so-called "brittle diabetes". CP patients are at increased risk of hypoglycemia, partly because of poor glycogen reserve due to malabsorption resulting from severe exocrine insufficiency.

Pancreatic endocrine insufficiency leading to diabetes usually occurs late in the natural history of CP. The prevalence of diabetes-related to the pancreatopathies is usually underestimated because it is often misclassified as either type 1 or type 2 diabetes. A study from Europe has shown the prevalence of type 3c diabetes to be around 9% among different diabetes populations[2]. About 80% of long-standing CP patients develop diabetes[3]. The prevalence of diabetes is much higher in fibro-calculous pancreatic diabetes (FCPD) typically found in the Indian subcontinent. Pancreatic islets are constituted by various cells: alpha cells secrete glucagon; beta-cells secrete insulin; delta cells secrete somatostatin and pancreatic polypeptide (PP) cells secrete PP. Progressive inflammation and fibrosis lead to atrophy of the pancreas and acinar cell death, which together culminate in pancreatic exocrine insufficiency. Nonetheless, endocrine insufficiency soon follows. However, the mechanism behind this progressive islet cell damage has remained an active area of research. Hence, we searched the evidence available on islet cell dysfunction in CP and summarized the evidence in this review.

LITERATURE SEARCH AND STUDY SELECTION

We searched the literature using the following key search terms: "islet cell" [AND] "chronic pancreatitis"; "alpha cell" [AND] "chronic pancreatitis"; "beta cell" [AND] "chronic pancreatitis"; "insulin" [AND] "chronic pancreatitis"; "glucagon" [AND] "chronic pancreatitis"; "incretin" [AND] "chronic pancreatitis"; "GLP-1" [AND] "chronic pancreatitis"; "GIP" [AND] "chronic pancreatitis"; "beta cell" [AND] "alpha cell" [AND] "chronic pancreatitis"; "islet transplantation" [AND] "chronic pancreatitis" [AND] "beta cell". Two authors [AR, JPS] independently searched the literature in PubMed. The search was restricted to English language articles and was performed from inception up to January 2020. We also looked for references in the

individual articles for their suitability and included them in this review if found to be appropriate. Studies which evaluated islet cell function in patients with CP in a comprehensive way were selected by the authors to be included in this review [JPS, SKK, DBN].

ALPHA CELL DYSFUNCTION IN CP

There has been a renewed interest in alpha cell dysfunction in both type 1 and type 2 diabetes. Alpha cell dysfunction has also been implicated in the pathogenesis of CP related diabetes (Figure 1). The destruction of beta-cell mass is higher when compared to alpha cells in patients with CP[4], which may result in higher glucagon levels in these patients. This destruction of islet cell mass occurs relatively later in the disease process. Studies have shown that alpha cell numbers are not significantly decreased in CP patients as compared to control populations[4]. One report has shown that alpha cell mass can be increased in patients with CP[5].

Glucagon secretion in CP has been assessed in several studies using different dynamic methods such as oral glucose, intravenous (IV) arginine, and IV alanine (Table 1). Baseline plasma glucagon levels were shown to be either similar[6], reduced[7] or elevated[8] compared to healthy controls in different studies. Similarly, stimulated glucagon levels are also varied among different studies[8-10]. In the study by Lundberg *et al*[11], both basal and post-meal stimulated glucagon levels were shown to be higher in CP patients compared to a normal healthy control population. Interestingly, their patient cohort had a relatively early stage of pancreatitis and none of them had diabetes.

Glucose mediated glucagon suppression was also assessed by Mumme *et al*[12]. Similar to diabetes patients without pancreatitis, glucose-induced glucagon suppression was found to be impaired in CP patients with diabetes after an oral glucose tolerance test (OGTT). Moreover, glucagon levels were lower in response to hypoglycemia in CP patients with diabetes in a stepwise hypoglycemic clamp. This finding establishes the poor alpha cell function in CP patients, particularly those developing diabetes.

Since elevated glucagon is part of the first-line defense against hypoglycemia, the diminished glucagon response exposes a patient with CP and DM to the risk of severe hypoglycemia, particularly when the disease is quite advanced. Absence of the glucagon response following hypoglycemia was also shown by Larsen *et al*[13]. We previously demonstrated that glucagon was not suppressed following an oral glucose load in patients with chronic calcific pancreatitis (CCP) irrespective of their diabetes status[14]. This suggests that the ability of alpha cells to suppress glucagon secretion in response to glucose is significantly impaired in CCP patients. In an another study by Schrader *et al*[15], it was found that the glucose-induced glucagon suppression was decreased after partial pancreatectomy. They found a trend of lower baseline glucagon after surgery. However, glucagon suppression was 22% after surgery as compared to 39% before surgery as shown by the OGTT. Interestingly, this impaired glucagon response was correlated with a reduction in insulin secretion but not with the elevated glucose level. They postulated that this alpha cell dysfunction is due to decreased beta cell mass. However, some studies have reported normal arginine stimulated glucagon response in CP patients with or without diabetes[16].

Another important consideration is whether this elevated glucagon is from outside the pancreas. Lund and colleagues[17] have shown evidence of extra-pancreatic glucagon in pancreatectomized patients as compared to normal healthy controls. They showed that hyperglucagonemia was seen after oral glucose but not during an IV isoglycemic glucose infusion in pancreatectomized patients. This suggests that CP patients with pancreatic atrophy may have elevated plasma glucagon level, which is gut derived. The possible mechanism for this may be due to a shift in the L-cells of the intestine towards secretion of more glucagon (mediated by prohormone convertase 2 enzyme) in the absence of pancreatic alpha cells. The stimulus for L-cells may be an altered delivery of nutrients including glucose secondary to the distorted anatomy of the small intestine, particularly after surgery. This area needs to be further clarified in future studies involving CP patients.

Table 1 Summary of the studies that assessed glucagon response in chronic pancreatitis

Ref.	Population characteristics	Method used	Key findings
Mumme *et al*[12], 2017	(1) Patients with diabetes due to CP; (2) Patients with type 2 diabetes without CP; and (3) NGT patients without CP	(1) OGTT; (2) Hyperinsulinemic, stepwise hypoglycemic clamp	(1) Higher fasting glucagon levels and an initial rise of glucagon after the OGTT in both groups with diabetes compared to the healthy group; and (2) Lower glucagon levels in both groups with diabetes after hypoglycemia in the clamp study
Kumar *et al*[14], 2018	Chronic calcific pancreatitis: pre- and post-Frey's procedure	OGTT	Before surgery: Elevated glucagon level at 60- and 120-min post OGTT compared to the fasting state
Lundberg *et al*[11], 2016	Non-diabetic patients with CP and healthy controls	(1) MMTT; and (2) FSIVGTT	(1) Elevated glucagon levels (total area under curve) in CP patients at both basal and post-stimulation state; and (2) No difference in basal to peak increment glucagon levels between the groups
Knop *et al*[38], 2010	(1) CP patients with NGT; (2) CP patients with IGT; (3) CP patients with DM; and (4) Normal healthy controls	(1) OGTT; and (2) IVGTT	(1) Similar fasting mean glucagon in all the groups; (2) During OGTT: No increase in glucagon level in the CP + NGT group; increased glucagon up to 60 min in the CP + IGT and CP + DM groups; a small early rise in glucagon which was suppressed later in the healthy group; and (3) During FSIVGTT, AUC for glucagon was higher in the CP + DM group compared to normal controls
Larsen *et al*[6], 1988	(1) Type 1 diabetes; (2) Insulin dependent diabetes secondary to CP; and (3) Normal healthy controls	(1) IV Glucagon; (2) IV Arginine infusion; and (3) Mixed meal test	No difference in baseline glucagon or stimulated glucagon levels between the groups with diabetes
Kannan *et al*[8], 1979	CP patients and healthy control group	(1) 50 g OGTT; and (2) L-arginine stimulation	(1) Elevated basal fasting glucagon and higher glucagon levels during the OGTT in CP patients compared to controls; and (2) An early rise in glucagon after L-arginine stimulation in CP patients compared to normal patients
Donowitz *et al*[10], 1975	CP group and healthy control group	IV L-alanine infusion	(1) Lower basal glucagon levels in CP patients; and (2) No rise in glucagon level after alanine stimulation in CP patients compared to normal controls

AUC: Area under curve; CP: Chronic pancreatitis; DM: Diabetes mellitus; FSIVGTT: Frequently sampled intravenous glucose tolerance test; IGT: Impaired glucose tolerance; IV: Intravenous; IVGTT: Intravenous glucose tolerance test; MMTT: Mixed meal tolerance test; NGT: Normal glucose tolerance; OGTT: Oral glucose tolerance test.

BETA-CELL DYSFUNCTION IN CP

Beta-cell destruction and consequently, insulin deficiency, has been viewed as the most important mechanism for the development of DM in CP (Figure 1). Meier *et al*[18] showed that the destruction of 65% of beta cells was associated with diabetes in CP patients. Postprandial hyperglycemia is more directly related to the reduction in beta-cell mass. Fasting hyperglycemia, which is more related to insulin resistance usually develops when beta-cell mass is significantly reduced. Schrader *et al*[4] reported a 29% reduction in beta-cell area in CP patients and in their study, one-third of patients had diabetes as compared to controls. A significant reduction in beta-cell mass has also been reported in patients with advanced CP without diabetes[19].

The presence of beta-cell dysfunction, in addition to reduced beta-cell mass is also very important in the development of DM in CP. The residual beta cells cannot function effectively in an environment of significant inflammation and fibrosis seen in CP. An *in vitro* analysis has shown that beta-cells retain only 53% of glucose-stimulated insulin secretive function in advanced CP patients without diabetes[19]. Lundberg *et al*[11], showed significantly lower mean disposition index (a composite
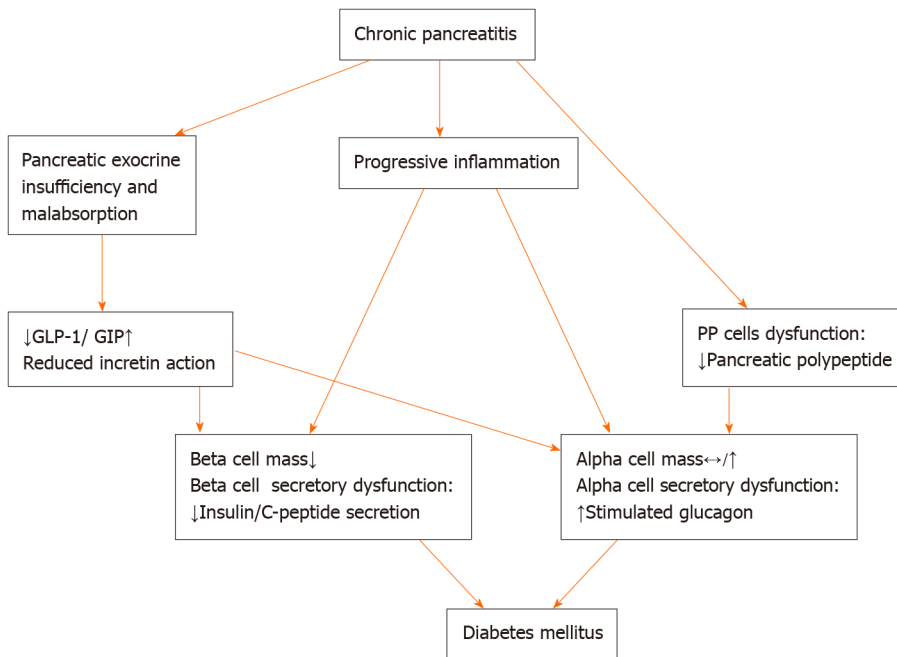
Figure 1 Mechanisms of islet cell dysfunction in patients with chronic pancreatitis. GLP-1: Glucagon-like peptide 1; GIP: Glucose-dependent insulinotropic polypeptide; PP: Pancreatic polypeptide.

marker of insulin secretion) after a frequently sampled intravenous glucose tolerance test in CP patients as compared to controls. However, following a mixed meal tolerance test (MMTT), a low C-peptide at 30 min was the only significant difference between CP and control patients. Interestingly, they also showed that calcific pancreatitis patients have a greater reduction in insulin secretion from beta cells when compared to non-calcific pancreatitis patients. This may imply that pancreatic calcification occurs in relatively advanced stages of pancreatitis.

FCPD is a distinct entity particularly prevalent in South India[20]. FCPD occurs in the 3rd or 4th decade of life and is often difficult to treat because of its brittleness. The mechanism of development of diabetes in FCPD is different when compared to other causes of CP[21]. Arginine stimulated C-peptide was found to be significantly lower in FCPD patients, but tropical calcific pancreatitis (TCP) patients without diabetes showed a normal response[16]. However, in North Indian TCP patients with mild dysglycemia, decreased beta-cell function was noted to be the major factor[22]. In our study[14], beta-cell function, as measured by insulin secretion sensitivity index-2 (another composite measure of insulin secretion) was lower in a group of CCP patients with DM compared to CCP patients with prediabetes or normal glucose tolerance (NGT).

PP CELL DYSFUNCTION IN CP

PP deficiency in CP has been observed in several studies. The most compelling evidence comes from glucose clamp studies, which showed the effect of PP deficiency in CP[23]. Seymour *et al*[24] showed that PP deficiency causes a reduction in the number of insulin receptors in the liver without altering insulin affinity. PP deficiency has been observed mostly in the postprandial state. A recent study[25] did not find any difference in fasting PP between CP patients with pancreatic adenocarcinoma and normal healthy controls irrespective of their glycemic status.

Interestingly, PP administration in CP patients reversed hepatic insulin resistance, confirming its role in CP related DM[23,24]. Subsequently, a randomized controlled trial of 72-h PP infusion showed significant improvement in insulin sensitivity in CP patients with diabetes[26]. Considering this evidence, an absent response of PP following a mixed meal was considered to be pathognomonic of CP related diabetes by a group of experts[27]. However, further studies are required to identify the effect of PP in CP patients. PP also suppresses glucagon secretion from alpha cells. This action is mediated by the PPYR1 receptor present in the islet alpha cells of both humans and

mice[28]. Since PP deficiency in CP has been demonstrated in different studies, it is possible that this suppressive effect on alpha cell glucagon secretion is lost in CP patients thereby resulting in hyperglucagonemia (Figure 1).

DELTA CELL DYSFUNCTION IN CP

Studies on somatostatin secreting delta cells are scarce and their exact role in CP has not been established. The study by Larsen *et al*[6] showed higher somatostatin levels following a mixed meal and arginine stimulation in diabetes secondary to pancreatitis as compared to type 1 diabetes and healthy controls. It was postulated that higher somatostatin levels may help to lower blood glucose level in patients with CP. The mechanism suggested was an inhibitory effect of somatostatin on both insulin and glucagon secretion. Somatostatin may also delay glucose absorption from the gut.

MECHANISMS OF ISLET CELL DYSFUNCTION IN CP

Disruption in the interaction between alpha and beta cells

Alpha cell secretion of glucagon is indirectly controlled by several mechanisms and these are perturbed in CP. One such mechanism is a beta cell defect leading to less insulin secretion in CP. Insulin suppresses glucagon during hyperglycemia and reciprocally, glucagon levels rise when insulin levels decline during hypoglycemia[29]. This switching mechanism may be lost in CP as progressive beta-cell failure is an established feature of CP. However, recent studies in animal models have shown that glucagon has potentiating action on beta cells to secrete more insulin, particularly in the postprandial state[30]. It is possible that hyperglucagonemia observed in CP is a compensatory response to falling insulin levels due to beta-cell loss.

Altered incretin axis in CP

Incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are secreted from L- and K-cells of the small intestine, respectively. Both GLP-1 and GIP physiologically regulate glucose metabolism by increasing insulin secretion *via* G-protein coupled receptors in beta-cells. However, GLP-1 suppresses glucagon secretion from alpha cells, whereas GIP augments glucagon secretion in the presence of hyperglycemia[31,32]. The reduced incretin hormone effect is a well-documented pathophysiological abnormality in type 2 diabetes[32].

The reduced incretin effect has been demonstrated in different studies in CP patients (Figure 1). However, whether this is primarily due to the effect of CP per se or due to the development of diabetes in CP patients is unclear. Vilsbøll *et al*[33] showed that the late phase insulin response (30-120 min) to GIP is particularly impaired in CP patients, whereas the response to GLP-1 was preserved in both the first and second phases. This difference was attributed to different post-receptor signaling between GIP and GLP-1, although they act through the same G-protein coupled receptor. The late phase insulin response (30-120 min) to GIP and not to GLP-1 infusion was shown to be impaired in CP patients with diabetes compared to CP patients with NGT[34].

Knop *et al*[35] compared CP patients with DM, CP patients with NGT, type 2 diabetics and healthy controls. They found a significantly lower incretin effect [measured by 100% × (β-cell secretory response to OGTT - intravenous β-cell secretory response)/β-cell secretory response to OGTT] in CP patients with diabetes, whereas CP patients without hyperglycemia had similar incretin hormones to the healthy population. However, basal GLP-1 was higher in CP patients with diabetes and type-2 diabetes patients. Importantly, beta-cell function was found to be similar in all four groups implying that the reduced incretin effect may be a consequence of the development of diabetes itself.

However, Lundberg *et al*[11] found no significant difference in either GLP-1 or GIP levels during MMTT in CP patients. Hornum *et al*[36] also did not find any difference in GIP response following a mixed meal in CP patients with pancreatic exocrine insufficiency compared to healthy subjects. Nevertheless, they showed an increased GLP-2 response in CP patients. This correlated with a higher superior mesenteric arterial flow. The incremental GLP-2 was possibly due to the easy access of more nutrients to the distal intestine stimulating GLP-2 secretion as a result of quick transit in CP patients. At present, the clinical role of GLP-2 is yet to be established in the

pathogenesis of diabetes, and in CP patients.

The role of incretin hormones is also implicated in the pathogenesis of alpha cell abnormality in CP. GLP-1 suppresses glucagon, whereas GIP has the opposite effect on glucagon[37]. Interestingly, Knop *et al*[38] demonstrated that glucagon levels were elevated in the first 60 min following the OGTT, but glucagon was suppressed during the IVGTT in CP patients. Importantly, glucagon suppression deteriorated throughout the spectrum of diabetes in CP patients. Glucagon suppression was low in CP patients with NGT, absent in CP with impaired glucose tolerance and glucagon levels were paradoxically elevated in CP with frank DM. The authors found that both basal and stimulated GIP response was higher in CP patients with DM, but GLP-1 levels were similar to the controls. This suggests that a change in the delicate balance between stimulatory and inhibitory incretin hormones that regulate glucagon secretion from alpha cells is an important contributor to hyperglucagonemia. However, Lund *et al*[17] found a significantly higher GLP-1 response during the OGTT in pancreatectomized patients compared to normal controls, but no difference in GIP response was seen. This area requires further studies to analyze the contribution of the extent of incretin hormone defect in alpha cell dysfunction.

CP is a state of malabsorption leading to steatorrhea as a result of pancreatic exocrine insufficiency. Both nutrient absorption and assimilation are important drivers of adequate incretin secretion (Figure 1). In an elegant study by Knop *et al*[39], it was found that CP patients with pancreatic exocrine insufficiency had higher GLP-1 and GIP responses to a mixed meal when the patients were supplemented with pancreatic enzymes. This higher incretin response was also associated with higher insulin secretion. A comparable result of increased GIP was shown previously by Ebert *et al*[40]. Similarly, higher GLP-2 levels after ingestion of a mixed meal were noted in CP patients when supplemented with pancreatic enzymes[41]. This is an active area of research. Pancreatic enzyme replacement therapy in CP and its effect on glucose homeostasis needs to be clarified in future studies. Studies are lacking in this area and whether enzyme supplementation itself improves glycemic control *via* the increased incretin effect or improved glycemic control per se leads to improved incretin response is still debated. Moreover, studies are also needed to identify how altered gut motility affects incretin hormones and glucose homeostasis in CP patients.

Dysregulation of amino acid metabolism

Another important consideration is the altered amino acid metabolism in CP. Amino acids are important mediators of the "liver-alpha cell axis". Increased hepatic resistance to glucagon increases the levels of certain amino acids and that, in turn, stimulates glucagon secretion from alpha cells[42]. It was recently shown that glucagon resistance in the liver increases the production of alanine, causing hyperglucagonemia further resulting in elevated glucose levels[43]. Indeed, the "glucagon-alanine index" is suggested to be a marker of glucagon's biological effect.

Abnormalities in amino acid metabolism have already been described in CP. It was found that the concentration of citrulline, gamma-aminobutyric acid, taurine, and aspartic acid were significantly decreased in CP patients[44]. On the other hand, hepatic steatosis has been described in pancreatectomized patients which may also cause elevated amino acids[45]. Thus, the contribution of disturbed amino acid metabolism on elevated glucagon level is yet to be established. Therefore, this area requires further active research to establish the relationship between hepatic steatosis, alpha cell dysfunction and disturbed amino acid metabolism in CP patients.

Chronic inflammation

CP is currently viewed as a progressive fibro-inflammatory disorder. Persistent inflammation is found in early CP and is more pronounced in established CP. This finally results in fibrosis of the pancreas with exocrine insufficiency, islet cell dysfunction, development of diabetes, and pancreatic carcinoma at the advanced stage[46] (Figure 1). It has also been suggested by Lundberg *et al*[11], that alpha cells present in the islet are under stress due to chronic inflammation and secrete higher amounts of glucagon until the disease reaches an advanced stage, when the alpha cell mass/secretory function starts to decline resulting in hypoglucagonemia. The pancreatic inflammation in CP also leads to altered sensitivity of alpha cells to oral glucose resulting in decreased glucagon suppression as suggested by Knop *et al*[38].

Beta-cell dysfunction usually occurs late in this process possibly due to a lack of TNF-related apoptosis-inducing ligand and apoptotic receptor (CD95)[47]. However, persistent inflammation and subsequent changes in the intra-islet cytokine milieu may adversely affect the intrinsic signaling machinery of beta cells, thus resulting in beta cell dysfunction and less insulin secretion[48]. In CP with autoimmune etiology, CD8+ T

cell-mediated beta cell dysfunction was described earlier[49]. Talukdar *et al*[50] showed that pancreatic islet cells in CP patients with DM are infiltrated with Th1 cells and this correlated with the increased rate of beta-cell apoptosis in this group of patients. The same study reported increased signal transducer and activator of transcription 1 or decreased pancreas and duodenal homeobox gene 1 (PDX-1) expression in CP patients with diabetes. The intra-islet increase in the interferon-gamma results in the reduction of PDX-1 expression and finally, beta-cell dysfunction.

Another important concept is beta cell dedifferentiation, wherein the mature beta-cells regress to more like precursor cells, which are less glucose-sensitive. A recent study by Sun *et al*[51] showed that CP patients without diabetes had a higher percentage of dedifferentiated cells in their islets (10.4% *vs* 3.6%) as compared to normal controls. Importantly, the beta-cell apoptosis rate in CP patients with DM was similar to the normal population. Interestingly, this finding is strongly correlated with islet inflammation and fibrosis associated with atrophy. This shows that the direct effect of inflammation plays an important role in beta cell dysfunction even in the early stages of CP.

Role of pancreatic stellate cells

Stellate cells have been identified in pancreatic islets and their role in chronic progressive fibrosis of the pancreas in type 2 diabetes has been described recently[52]. However, its effect on islet cells remains uncertain. Activated stellate cell-induced dysfunction in pancreatic beta-cells has been described recently in a few animal studies[53,54] although human studies are lacking.

DIFFERENCE IN ISLET CELL FUNCTION BETWEEN CP WITH DM *VS* CP WITH NGT

The development of type 2 DM is seen as a continuum of different stages from NGT to prediabetes to frankly elevated blood glucose to satisfy the criteria for diabetes. It is intriguing to look at the changes in islet cell function in CP patients as they gradually progress to diabetes from normal glucose levels. As already described, early dysfunction in insulin secretion and glucagon suppression is seen in CP patients without diabetes[11]. Indeed, it has been shown that beta cell function and insulin secretion is lower in CP patients with DM compared to CP patients with NGT[14,38]. CP patients with prediabetes are intermediate in terms of beta cell secretary function[14,38]. Although our study[14] showed no difference in glucagon suppression between CP subjects with NGT, prediabetes and diabetes groups at baseline, Knop *et al*[38] clearly demonstrated a rise in glucagon level in a continuous manner across NGT to diabetes in CP. Moreover, CP patients with DM have significantly low GIP stimulated late insulin secretion (20-120 min) compared to CP with NGT who had a significantly greater insulin response to GIP. Taken together these findings show that the development of diabetes in CP is related to alterations in both alpha and beta cell function, whereas islet cell function is maintained in CP patients with NGT.

EFFECT OF DIFFERENT INTERVENTIONS ON ISLET CELL FUNCTION IN CP

It is likely that patients with CP will undergo interventional procedures such as pancreatectomy (including Frey's procedure) for various reasons including intractable pain. Indeed, recent studies have shown that pancreatic surgery is a strong and independent risk factor for the development of diabetes in CP patients[55,56]. It is of great interest to determine the changes in islet cell function following an intervention and how these changes translate into the development of diabetes.

Menge *et al*[57] showed a 50% decline in insulin secretion after a 75-g OGTT in CP patients undergoing hemi-pancreatectomy. Interestingly, follow-up of these participants (*n* = 10) for 3 years (range 2.2-3.8 years) showed a considerable improvement in the level of plasma insulin and C-peptide, although preoperative basal values were not reached[58]. The authors attributed this limited functional recovery of beta cells to improvement in the inflammatory milieu and gastric motility in the long term as compared to the immediate postoperative period. Importantly, in the immediate postoperative period, it was found that resection of the pancreatic tail was associated with significant worsening of glycemia after glucose challenge,

whereas pancreatic head resection resulted in lower glycemic excursion. This finding suggests that different procedures have a different impact on postoperative beta cell function. Similar findings of initial deterioration followed by relatively stable beta cell function up to 36 months were also demonstrated in an earlier study[59]. On the contrary, a recent study[60] showed that CP patients who underwent a surgical drainage procedure (Puestow, Frey, or similar procedure) had a rapid decline in C-peptide level during a mixed meal test. However, studies have also reported no change in beta cell function in subjects with CP following surgical interventions such as resection and drainage[14,61].

Alpha cell function is also affected following surgery in patients with CP. Altered glucagon suppression following surgery has been described in a few studies[14,15]. Fasting lower glucagon after surgery probably reflected a loss of alpha cell mass[15] during the procedure, but there was a significant increase in glucagon secretion post-glucose challenge after surgery[14,15]. This could reflect the possible effect of impaired beta cell function on alpha cells as insulin secretion is also simultaneously impaired. Taken together, it is evident that beta cell function declines after surgery and it may stabilize in the long-term, but at a lower level compared to the presurgical state, and there is definite evidence of alpha cell dysfunction following surgical procedures in CP.

Another issue that needs to be considered in patients with CP is assessment of the functional preservation of islet cell function following total pancreatectomy and autologous islet transplantation (TP-AIT). A detailed discussion on this topic can be found elsewhere[62,63]. Roughly one third of patients maintain insulin independence following TP-AIT at around two years post-transplantation and a significant proportion of patients require a reduced insulin dose[64,65]. However, the percentage of patients achieving insulin independence declines as time progresses. In some studies, almost 50% of patients achieved insulin independence at a median follow- up of approximately two years[66].

The formal assessment of beta cell functionality is by fasting insulin, C-peptide, glycosylated hemoglobin (HbA1c) and importantly by the requirement of exogenous insulin for glycemic control. Recently Ali and colleagues showed that there is a gradual decrease in post-meal stimulated insulin and C-peptide following islet transplant and more so after 6 months of follow-up[67]. They also demonstrated a gradual decline in the beta 2 score (a composite score to assess islet viability based on fasting glucose, fasting C-peptide, insulin dose and HbA1C) after transplantation. However, the study by Robertson *et al*[68] demonstrated no difference in insulin and C-peptide response to glucose potentiated acute arginine stimulation in CP patients after TP-AIT (follow up of 1-8 years). The beta cell response strongly correlated with the number of transplanted islets. These authors also observed that transplanted alpha cells showed a normal response to arginine stimulation and glucagon was appropriately suppressed after glucose infusion. This result suggests that alpha cells function normally after islet transplant. However, in an earlier study, it was shown that the glucagon response to hypoglycemia was impaired during a 3-h hypoglycemic hyperinsulinemic clamp study in recipients of autologous islet transplant in CP after pancreatectomy[69].

EFFECTS OF ANTI-HYPERGLYCEMIC DRUGS ON ISLET CELL FUNCTION IN PATIENTS WITH CP

There are very few studies in the literature which have evaluated the effect of antidiabetic drugs on islet cell function in CP patients. Of the drugs used to treat diabetes in CP, the effect of thiazolidinediones (TZDs) has been noted, particularly in animal studies. TZDs have been shown to limit the progression of pancreatitis by inhibiting the fibrogenic action of pancreatic stellate cells in rat models[70]. However, human studies on the effect of TZDs on islet cells are lacking. Side effects such as fluid retention, bone loss[71] in the face of malnutrition in CP patients are important and TZDs should be used cautiously in CP.

A randomized controlled trial did not show any difference in insulin and C-peptide response in sitagliptin treated patients with CP who underwent TP-AIT in comparison to placebo after up to 18 months of treatment[72]. There was no difference in insulin dependence or insulin dose reduction either. There is good evidence that GLP-1 analogues increase beta cell mass and prevent apoptosis in rodent models[73,74]. However, the effect of incretin therapy on human pancreatic islet cell morphology was not marked in diabetes patients who received incretin therapies as compared to those

who did not[75]. Importantly, the use of these agents is not suitable in patients with CP due to the risk of precipitating pancreatitis itself[76] and some histological evidence of cellular changes that may increase the risk of neoplasia[77].

CONCLUSION

CP is a progressive inflammatory disorder leading to islet cell disturbances and the subsequent development of diabetes. The disease pathology is complex and is characterized by dysregulation of islet cells. An ongoing inflammatory milieu affects different aspects of the functionality of islet cells. A critical decrease in beta cell mass as well as a decline in insulin and C-peptide secretion are the classic defects found in CP. At baseline, patients with CP but without diabetes have adequate beta cell function which is progressively lost along with the development of prediabetes to diabetes. There is also evidence of inappropriate glucagon secretion in CP patients more so after surgical procedures; however, their impact on glycemic control remains to be determined. The source of this elevated glucagon needs to be confirmed in future studies. PP cells and delta cell functional abnormalities as well as altered secretion of incretin hormones (GLP-1/GIP) are evident in CP and significantly contribute to alpha and beta cell dysregulation.

The different surgical procedures performed in patients with CP and the antihyperglycemic drugs used to treat diabetes associated with CP also affect islet cell function. Surgical intervention in CP can lead to stabilization of beta cell decline albeit at a lower level than the presurgical state. Islet cell transplantation is promising in the management of diabetes in CP following total pancreatectomy. It seems to be an effective measure to curtail the risk of diabetes development by maintaining adequate beta cell function. Newer therapies targeting alpha cell function and beta cell regeneration would be useful in the management of pancreatic diabetes in the near future.

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