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**Islet cell dysfunction in patients with chronic pancreatitis**

Roy A *et al*. Islet cell dysfunction in patients with CP

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**Abstract**

Chronic pancreatitis (CP) is characterised by progressive inflammation and fibrosis of the pancreas that eventually leads to pancreatic exocrine and endocrine insufficiency. The diabetes in the background of CP is very difficult to manage because of high glycaemic variability and concomitant malabsorption. Progressive beta cell loss leading to insulin deficiency is the cardinal mechanism behind diabetes development in CP. Alpha cell dysfunction leading to deranged glucagon secretion has been described in different studies using a variety of stimulus in CP. However, the emerging evidences are 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, the secretion of the incretin hormones like glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide is dysregulated. This contributes towards islet cell disturbances significantly. Persistent and progressive inflammation with changes in the function of other cells of islet like delta cells and pancreatic polypeptide cells are also implicated in CP. In addition, the different surgical procedures done in patients with CP and antihyperglycemic drugs used to treat diabetes associated with CP also affect islet cell function. Hence, different factors like chronic inflammation, dysregulated incretin axis, surgical interventions and ant-diabetic drugs all together 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

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**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 done 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 slowly 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 as type 3c diabetes[1]. Diabetes mellitus (DM) due to CP is characterized by predominant post-prandial hyperglycemia and fasting hyperglycemia usually comes 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 population[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 of various cells: alpha cell secretes glucagon; beta-cell secretes insulin; delta cell secretes somatostatin and pancreatic polypeptide (PP) cell secretes PP. Progressive inflammation and fibrosis lead to atrophy of pancreas and acinar cell death, which altogether culminates into 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 about islet cell dysfunction in CP and have summarized them in this review.

**LITERATURE SEARCH AND STUDY SELECTION**

We have searched the literature with the following search keys: “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 and search was performed till January 2020 from the inception. We also looked for references in the individual articles for the suitability and included in this review if found to be appropriate. The studies which have evaluated the islet cell function in patients with CP in a comprehensive way was selected by the authors to be included for 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 the 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 decreased significantly 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 like 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 control in different studies. Similarly, the stimulated glucagon levels is 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 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 hypoglycaemia in CP patients with diabetes in a stepwise hypoglycaemic clamp. This finding establishes the poor alpha cell function in CP patients, particularly those developing diabetes.

Since elevated glucagon is among the first-line defence against hypoglycaemia, the diminished glucagon response exposes a patient with CP and DM to the risk of severe hypoglycaemia, particularly when the disease is quite advanced. Absence of glucagon response following hypoglycaemia was also shown by Larsen *et al*[13]. From our group, we have demonstrated that glucagon was not suppressed following 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 done 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. But glucagon suppression was 22% after surgery as compared to 39% before surgery during OGTT. Interestingly, this impaired glucagon response was correlated with 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 coming from the outside pancreas. Lund and colleagues has[17] shown the evidence of extra-pancreatic glucagon in pancreatectomised patient as compared to normal healthy controls. They have shown that hyperglucagonemia was seen after oral glucose but not during an IV isoglycemic glucose infusion in pancreatectomised patients. This suggest that CP patients with pancreatic atrophy may have elevated plasma glucagon level, which is gut derived. The possible mechanism may be due to a shift of 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 the 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.

**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] have shown that the destruction of 65% of the beta cells was associated with diabetes in CP patients. Postprandial hyperglycaemia is more directly related to the reduction of beta-cell mass. Fasting hyperglycaemia, which is more related to insulin resistance usually develops when beta-cell mass is reduced significantly. Schrader *et al*[4] reported a 29% reduction in beta-cell area in CP patients and in their study, one-third patients had diabetes as compared to controls. 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. In-vitro analysis has shown that beta-cell retains 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 marker of insulin secretion) after frequently sampled intravenous glucose tolerance test in CP patients as compared to controls. However, following 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 more reduction in insulin secretion from beta cells when compared to non-calcific pancreatitis. This may imply that pancreatic calcification occurs in relatively advanced stage of pancreatitis.

FCPD is a distinct entity particularly prevalent in South India[20]. FCPD results in diabetes 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 dysglycaemia, 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 the glucose clamp studies showing the effect of PP deficiency in CP[23]. Seymour *et al*[24] have shown that PP deficiency causes a reduction in the number of insulin receptors in the liver without altering the 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 control irrespective of their glycaemic status.

Interestingly, PP administration in CP patients reversed the 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 these 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 look for the effect of PP in CP patients. PP also suppresses glucagon secretion from the alpha cells. This action is mediated by the PPYR1 receptor present in the islet alpha cell 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 and thereby resulting in hyperglucagonemia(Figure 1).

**DELTA CELL DYSFUNCTION IN CP**

Studies on somatostatin secreting delta cells are scarce and its exact role in CP has not been established. The study by Larsen *et al*[6] had shown 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 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 beta cell defect leading to less insulin secretion in CP. Insulin suppresses glucagon during hyperglycaemia and reciprocally, glucagon levels rise when insulin levels decline during hypoglycaemia[29]. This switching mechanism may be lost in CP as progressive beta-cell failure has been an established feature of CP. However, recent studies in animal models have shown that glucagon has potentiating action on the beta cell 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 like glucagon-like peptide type 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 receptor in the beta-cell. However, GLP-1 suppresses glucagon secretion from the alpha cell, whereas GIP augments glucagon secretion in the presence of hyperglycaemia[31,32]. Reduced incretin hormone effect is a well-documented pathophysiological abnormality in type 2 diabetes[32].

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] have shown 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 signalling 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 diabetes and healthy controls. They found a significant 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 hyperglycaemias had similar incretin hormones as the healthy population. However, basal GLP-1 was higher in CP patients with diabetes and type-2 diabetes patients. Importantly, the beta-cell function was found to be similar in all the four groups implying that reduced incretin effect may be a consequence of the development of diabetes itself.

However, Lundberg *et al*[11] found no significant difference in neither 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 liquid 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 the higher superior mesenteric arterial flow. The incremental GLP-2 was possibly due to the easy access of more nutrients to 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, more so 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 OGTT, but glucagon was suppressed during 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, lost in CP with impaired glucose tolerance and glucagon levels were paradoxically elevated in CP with frank DM. They actually found that both basal and stimulated GIP response was higher in CP patients with DM but GLP-1 levels were similar as compared to controls. This suggests that change in the delicate balance between stimulatory and inhibitory incretin hormones that regulate glucagon secretion from alpha cells is an important contributor towards the hyperglucagonemia. Lund *et al*[17] however found a significant higher GLP-1 response during OGTT in pancreatectomised patients compared to normal controls but no difference in GIP response was seen. This area requires further studies to analyse the contribution of the extent of incretin hormone defect towards 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 response to a mixed meal when the patients were supplemented by pancreatic enzymes. This higher incretin response was associated with higher insulin secretion also. 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 glycaemic control *via* increased incretin effect or improved glycaemic 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 certain amino acid levels and that, in turn, stimulates glucagon secretion from the alpha cell[42]. It has been recently shown that glucagon resistance in the liver increases the production of alanine, causing hyperglucagonemia further resulting in elevated glucose levels[43]. Indeed, “glucagon-alanine index” is suggested as a marker for 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 side, hepatic steatosis has been described in pancreatectomised patients which may also cause elevated amino acids[45]. So the contribution of the disturbed amino acid metabolism on elevated glucagon level is yet to be established. Thus, this area requires further active research to establish the relationship of 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. The persistent inflammation is found in early CP and is more pronounced in established CP. This finally results in fibrosis of 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 amount of glucagon until the disease reaches an advanced stage, when the alpha cell mass/secretory function start declining resulting in hypoglucagonemia. The pancreatic inflammation in CP also leads to altered sensitivity of the alpha cell to oral glucose resulting decreased glucagon suppression as suggested by Knop *et al*[38].

Beta-cell dysfunction usually occurs late in this process possibly due to lack of TNF-related apoptosis-inducing ligand and apoptotic receptor (CD95)[47]. But persistent inflammation and subsequent changes in the intra-islet cytokine milieu may adversely affect the intrinsic signalling machinery of beta cells, thus resulting in beta cell dysfunction and less insulin secretion[48]. In CP with autoimmune aetiology, CD8+ T cell-mediated beta cell dysfunction has been described earlier[49]. Talukdar *et al*[50] have shown 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 the beta cell dedifferentiation, wherein the mature beta-cell regress to more like a precursor cell, which is 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 islet (10.4% *vs* 3.6%) as compared to normal controls. Importantly, the beta-cell apoptosis rate in CP 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 part in beta cell dysfunction even in the early stages of CP.

***Role of pancreatic stellate cells***

Stellate cells have been identified in the pancreatic islet and their role in the chronic progressive fibrosis of the pancreas in type 2 diabetes has been described in recent times[52]. However its effect on islet cells remains uncertain. Activated stellate cell-induced dysfunction in the pancreatic beta-cell has been described recently in a few animal studies[53,54] though 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 the frankly elevated blood glucose to satisfy the criteria for diabetes. It is intriguing to look at the changes in the islet cell function in CP patients as they gradually progress to diabetes from normal glucose levels. As already described, an early dysfunction in insulin secretion and glucagon suppression is seen in CP patients without diabetes[11].Indeed, it has been shown that the beta cell function and insulin secretion is lower in the CP patients with DM group as compared to CP with NGT[14,38]. CP patients with prediabetes are intermediate in terms of beta cell secretary function[14,38]. Though our study[14] showedno difference in glucagon suppression between CP subjects with NGT, prediabetes and diabetes groups at baseline, Knop *et al*[38] clearly demonstrated a rise in the glucagon level in a continuous fashion 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 it is evident that development of diabetes in CP is related to alteration in both alpha and beta cell function whereas islet cell function is still maintained in CP patients with NGT.

**EFFECT OF DIFFERENT INTERVENTIONS ON ISLET CELL FUNCTION IN CP**

It is likely that patient with CP will undergo intervention procedures like 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 look for the changes in the islet cell function following an intervention and how this changes translates into development of diabetes.

Menge *et al*[57] have shown a 50% decline in insulin secretion after a 75-g OGTT in CP patients undergoing hemi pancreatectomy. Interestingly, follow up of the same 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, though it never reached the preoperative basal values[58]. The authors attributed this limited functional recovery of beta cells to the improvement in inflammatory milieu and gastric motility in the long term as compared to immediate postoperative period. Importantly, at immediate postoperative period, it was found that resection of pancreatic tail was associated with significant worsening of glycemia after glucose challenge whereas pancreatic head resection resulted in lower glycaemic excursion. This finding points towards the notion that different procedure have impact on the postoperative beta cell function differently. Similar finding of initial deterioration followed by relatively stable beta cell function up to 36 mo was also demonstrated in an earlier study[59]. On the contrary, a recent study[60] showed that CP patients who underwent surgical drainage procedure (Puestow, Frey, or similar procedure) had rapid decline in the C-peptide level during a mixed meal test. However, studies have also reported no change in the beta cell function in subjects with CP following operative intervention like resection and drainage[14,61].

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

Another issue that needs to be considered in patients with CP is the 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 lesser insulin dose[64,65]. However, the percentage of patients achieving insulin independence decline as time progresses. In some studies, almost 50 percent of patients achieved insulin independence at a median follow up of approximately two years[66].

The formal assessment of beta cell functionality is assessed by fasting insulin, C-peptide, glycosylated haemoglobin (HbA1c) and importantly by the requirement of exogenous insulin for glycaemic control. Recently Ali and colleagues have shown that there is a gradual decrease in the post meal stimulated insulin and C-peptide following islet transplant and more so after 6 mo 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, a 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 the transplanted islets. They also observed that transplanted alpha cells showed a normal response to arginine stimulation and glucagon was appropriately suppressed after glucose infusion. This result suggests normally functional alpha cell component following islet transplant. However, in an earlier study, it was shown that the glucagon response to hypoglycaemia was impaired during a 3-h hypoglycaemic hyperinsulinemic clamp study in recipients of autologous islet transplant in CP after pancreatectomy[69].

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

There are very few studies in the literature which have evaluated the effect of any antidiabetic drug on the islet cell function in CP patients. Among the drugs used to treat diabetes in CP, the effect of thiazolidinediones (TZD) has been noted, particularly in animal studies. TZDs have shown to limit the progression of pancreatitis by inhibiting the fibro-genic action of pancreatic stellate cell in rat models[70]. But human studies are lacking on the effect of TZDs on islet cell. Side effects like 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 of CP who underwent TP-AIT in comparison to placebo after up to 18 mo of treatment[72]. There was no difference in insulin dependence or insulin dose reduction either. There is good amount of evidence that GLP-1 analogue increases 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 who did not[75]. Importantly, the use of these agents is not suitable in patients with CP due to risk of precipitation of 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 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 the islet cells. A critical decrease in beta cell mass as well as decline in beta cell function of insulin and C-peptide secretion, is the classical defect found in CP. At baseline patients with CP but without diabetes have adequate beta cell function which is lost progressively along with the development of prediabetes to diabetes. There is also evidence of inappropriate glucagon secretion in CP patient more so after surgical procedure, however its impact on glycaemic control remains to be determined. The source of this elevated glucagon needs to be confirmed in future studies. PP cells and delta cell functional abnormality as well as altered secretion of incretin hormones (GLP-1/GIP) are evident in CP and contributes significantly towards alpha and beta cell dysregulations.

The different surgical procedures done in patients with CP and antihyperglycemic drugs used to treat diabetes associated with CP also affect islet cell function. Surgical intervention in CP can lead to stabilisation of beta cell decline albeit at a lower level than presurgical state. Islet cell transplantation holds promise 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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**Footnotes**

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**Figure Legends**

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**Figure 1 Mechanisms of islet cell dysfunction in patients with chronic pancreatitis.** GLP-1: Glucagon-like peptide type 1; GIP: Glucose-dependent insulinotropic polypeptide; PP: Pancreatic polypeptide.

**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; (3) NGT patients without CP | (1) OGTT; (2) Hyperinsulinemic, stepwise hypoglycemic clamp | (1) Higher fasting glucagon levels and the initial rise of glucagon after OGTT in both groups with diabetes compared to healthy group; (2) Lower glucagon levels in both groups with diabetes after hypoglycemia in 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 fasting state |
| Lundberg *et al*[11], 2016 | Non-diabetic patients with CP and healthy controls | (1) MMTT; (2) FSIVGTT | (1) Elevated glucagon levels (total area under curve) in CP patients at both basal and post-stimulation state; (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; (4) Normal healthy controls | (1) OGTT; (2) IVGTT | (1) Similar fasting mean glucagon in all the groups; (2) During OGTT: no increase in glucagon level in CP + NGT group; increased glucagon up to 60 min in CP + IGT and CP + DM groups; a small early rise of glucagon which was suppressed later in healthy group; (3) During FSIVGTT, AUC for glucagon was higher in CP + DM group in compared to normal controls |
| Larsen *et al*[6], 1988 | (1) Type 1 diabetes; (2) Insulin dependent diabetes secondary to CP; (3) Normal healthy controls | (1) I.V Glucagon; (2) I.V Arginine infusion; (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 gm OGTT; (2) L-arginine stimulation | (1) Elevated basal fasting glucagon and higher glucagon levels during OGTT in CP patients compared to controls; (2) The early rise of glucagon after L-arginine stimulation in CP patients compared to normal patients |
| Donowitz *et al*[10], 1975 | CP with healthy control groups | IV L-alanine infusion | (1) Lower basal glucagon levels in CP patients; (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.