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Incretins in fibrocalculous pancreatic diabetes: A unique subtype of pancreatogenic diabetes

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Abstract

Background: Studies evaluating endocrine and exocrine functions in fibrocalculous pancreatic diabetes (FCPD) are scarce.

Methods: Insulin, C-peptide, glucagon, incretin hormones (glucagon-like peptide 1 [GLP-1] and gastric inhibitory peptide [GIP]), and dipeptidyl peptidase IV (DPP-IV) were estimated in patients with FCPD (n = 20), type 2 diabetes mellitus (T2DM) (n = 20), and controls (n = 20) in fasting and 60 minutes after 75 g glucose.

Results: Fasting and post-glucose C-peptide and insulin in FCPD were lower than that of T2DM and controls. Plasma glucagon decreased after glucose load in controls (3.72, 2.29), but increased in T2DM (4.01, 5.73), and remained unchanged in FCPD (3.44, 3.44). Active GLP-1 (pmol/L) after glucose load increased in FCPD (6.14 to 9.72, $P = <.001$), in T2DM (2.87 to 4.62, $P < .001$), and in controls (3.91 to 6.13, $P < .001$). Median active GLP-1 in FCPD, both in fasting and post-glucose state (6.14, 9.72), was twice that of T2DM (2.87, 4.62) and 1.5 times that of controls (3.91, 6.13) ($P < .001$ for all). Post-glucose GIP (pmol/L) increased in all: FCPD (15.83 to 94.14), T2DM (21.85 to 88.29), and control (13.00 to 74.65) ($P < .001$ for all). GIP was not different between groups. DPP-IV concentration (ng/mL) increased in controls (1578.54, 3012.00) and FCPD (1609.95, 1995.42), but not in T2DM (1204.50, 1939.50) ($P = .131$). DPP-IV between the three groups was not different. Fecal elastase was low in FCPD compared with T2DM controls.

Conclusions: In FCPD, basal C-peptide and glucagon are low, and glucagon does not increase after glucose load. GLP-1, but not GIP, in FCPD increases 1.5 to 2 times as compared with T2DM and controls (fasting and post glucose) without differences in DPP-IV.

KEYWORDS

FCPD, fibrocalculous pancreatic diabetes, incretins, pancreatogenic diabetes

Highlights

- Incretins in pancreatogenic diabetes have been studied in chronic pancreatitis; however, incretins in fibrocalculous pancreatic diabetes (FCPD), a unique form of pancreatogenic diabetes, have not been explored previously.
- This study would significantly help in incretin biology in FCPD and may help bridge the knowledge gap in current understanding.

1 | INTRODUCTION

Fibrocalculous pancreatic diabetes (FCPD) refers to diabetes secondary to fibrocalculous pancreatopathy. This kind of diabetes falls in the category of a mixed bag of diseases which includes all types of diabetes secondary to diseases of the exocrine pancreas.[1-3] Currently, diabetes in the context of disease of the exocrine pancreas has been termed pancreoprivic diabetes.[4] A major body of evidence about pancreatogenic diabetes is in relation to diabetes secondary to major forms of chronic pancreatitis, pancreatic malignancies, cystic fibrosis, and pancreatic resection.[1] However, data related to FCPD, particularly with respect to the incretin physiology, are scarce.

Pancreatogenic diabetes as a group is associated with an impaired incretin effect. This is documented in chronic pancreatitis, but not in FCPD.[1] In contrast to type 2 diabetes mellitus (T2DM) where glucagon-like peptide 1 (GLP-1) secretion is diminished and there is resistance to the action of gastric inhibitory peptide (GIP),[5,6] subjects with pancreatogenic diabetes in general are sensitive to GLP-1, but GIP-induced late-phase insulin secretion is impaired similar to that in T2DM.[7] Secretion of GIP is impaired in subjects with steatorrhea due to alcoholic pancreatitis.[8] Plasma glucagon increases steeply after a glucose load in T2DM, but such a response was absent in FCPD.[9] However no study has evaluated basal or stimulated incretin hormone responses to oral glucose or meals in FCPD.

Subjects with chronic pancreatitis may develop an insufficiency of the exocrine pancreas. This may result in diminished entry of nutrients due to malabsorption which can eventually lead to absent or blunted incretin response to meals and reduce postprandial insulin secretion.[8] However, the pancreatic enzyme replacement therapy (PERT) with mixed meals to evaluate changes in glycemic state as well as in incretins, insulin, and glucagon yielded variable results. Thus, the impaired incretin response may actually be a consequence of diabetes rather than its cause.[10]

The objective documentation of insufficiency of the exocrine pancreas is difficult and controversial. Examination of stool collected over 72 hours following the intake of 100 g of oral fat daily is cumbersome, time-consuming, and not easily tolerated because of dyspepsia and worsening steatorrhea. However, pancreatic elastase remains stable during intestinal transit[11] and can be measured in feces by an enzyme-linked immunosorbent assay kit (ELISA). The use of fecal elastase does not require cumbersome stool collection or a special high-fat diet, and it has a high negative predictive value and a high sensitivity in moderate to severe disease when formed stools are analyzed.

We explored incretin responses in basal and oral glucose-stimulated state in FCPD and compared it with T2DM and normoglycemic subjects. We also measured dipeptidyl peptidase IV (DPP-IV) levels to exclude any alteration of incretins that could be explained by different levels of this enzyme. We propose that if the GLP-1 level is low, PERT might act better in this subgroup, whereas if the GLP-1 level is high, DPP-IV inhibitors will be infructuous.

2 | METHODS

We evaluated 20 consecutive subjects with FCPD, 20 subjects with T2DM, and 20 subjects with normal glucose tolerance. Diabetes was defined according to the American Diabetes Association criteria. The following criteria[12] by Mohan et al were used for diagnosis of FCPD/tropical pancreatic diabetes: (a) a history of recurrent abdominal pain from an early age; (b) pancreatic calculi seen on plain abdominal X-ray and confirmed by ultrasonography; (c) absence of history of alcoholism, gallstones, or hyperparathyroidism; and (d) diabetes diagnosed by the WHO criteria.

The study protocol was approved by the Ethical Committee of the Institute of Post-Graduate Medical Education & Research, Kolkata, West Bengal, India. The patients were informed about the study, and only those who gave informed written consent were included. Data on age, sex, socioeconomic status, dietary habits, family history, duration of diabetes, glycemic control, and treatment details were recorded.

All participants were 18 to 50 years of age. In the FCPD group, there were 7 male and 13 female patients. The mean body mass index (BMI) was 18.1 kg/m^2 and all of them were treated with insulin with a mean requirement of 22.4 units/d (range 16-42 units/d). Only seven patients were also on metformin, and four patients were receiving glimepiride in addition to insulin. The mean duration of diabetes was 5.1 years. The median glycosylated hemoglobin (HbA1c) was 8.12%. However, none of them were on pancreatic enzyme supplement.

In the T2DM group, there were 11 male and 9 female subjects. The mean BMI was 23.4 kg/m^2. The mean duration of diabetes was 5.2 years. All of them were on metformin. Seventeen persons were also receiving either glimepiride or gliclazide, and seven patients were also on pioglitazone. Four subjects were additionally receiving basal insulin. The median HbA1c was 7.8%.

Control subjects (11 males, 9 females) were chosen from among either their spouses or unrelated persons of the same age group and tested for their fasting blood sugar and HbA1c to rule out diabetes before inclusion in the study. The mean BMI was 21.7 kg/m^2.

All subjects were examined clinically and screened for micro- and macrovascular complications of diabetes. Insulin was stopped for 24 hours and oral hypoglycemic agents (OHA) for 48 hours before the tests.

Beta cell function was assessed by measuring insulin, taking serum from clotted vials and C-peptide from blood collected in ethylenediaminetetraacetic acid (EDTA) vials with the protease inhibitor aprotonin (5 μL/mL of blood). Alpha cell function was assessed by measuring glucagon from blood collected in EDTA vials with aprotonin (5 μL/mL of blood). Incretins were assessed by measuring GLP-1 and GIP from blood collected in EDTA vials with aprotonin (5 μL/mL of blood). All measurements were done in fasting state and 60 minutes after a 75-g glucose load. We chose these assessments to be done at 60 minutes as it was shown in previous studies that the peak of GLP-1, GIP, insulin, and C-peptide and the trough of glucagon in healthy individuals after oral glucose administration occur at around 60 minutes.[13] DPP-IV was measured from blood collected in EDTA vials with aprotonin (10 μL/mL of blood). All estimations were done by the ELISA method. Reagents for DPP-IV estimation were manufactured by RayBiotech (Peachtree Corners, Georgia). All other reagents were manufactured by Merck Millipore (Burlington, Massachusetts).

For GLP-1, the cleaved peptides, generally known as GLP-1 (7-36) amide and GLP-1 (7-37) are the forms of GLP-1 which are biologically active. The ELISA-based assay by Merck Millipore detects GLP-1 (7-36) amide and GLP-1 (7-37) isoforms using a 25-μL sample volume. The lower limit of detection is defined as the total active GLP-1 being 0.364 pmoL/L (0.12 pg/mL). The inter-assay and intra-assay precisions were 8% ± 4.8% and 7.4% ± 1.1%, respectively. The kit for human GIP measures total GIP levels, and this ELISA-based assay had a sensitivity of 1.65 pmoL/L (8.2 pg/mL). The inter-assay and intra-assay precisions were 1.8% to 6.1% and 3.0% to 8.8%, respectively.

Fecal elastase was also measured by the ELISA method. A fresh sample of stool was collected in a sterile container after proper labeling, immediately stored at 2 to 8°C, and tested within a week. About 30 to 100 g of stool was thoroughly mixed with extraction buffer and vortexed, and then the homogeneous mixture was allowed to settle for 15 to 30 minutes. The supernatant was then collected and mixed with washing solution and tested. After the ELISA reaction was over, the reading was taken using a wavelength of 450 nm within 10 minutes of stopping the reaction.

Fasting blood glucose was assessed from venous plasma glucose by the glucose oxidase-perioxidase method. We used 75 g of anhydrous glucose (G75, 75-g sachet [EMCURE Pharmaceuticals Limited, Pune, India], which is stated to continue anhydrous dextrose 75 g).

Incretins (both GLP-1 and GIP) and glucagon were expressed in pmol/L, C-peptide in nmol/L, and DPP-IV level in ng/mL. Insulin was expressed in mU/L and fecal elastase in μg/g of stool.

The results were analyzed by standard statistical tests using SPSS (v 21.0; SPSS Inc, Chicago, Illinois). Descriptive data were expressed as median with interquartile range (IQR). Comparison of values between fasting and post-glucose state within the same subject in each group were done by Wilcoxon's signed rank test. Comparison of data between different groups was carried out by a Kruskal-Wallis test.

3 | RESULTS

Twenty subjects with FCPD (7 males, 13 females), 20 subjects with T2DM (11 males, 9 females), and 20 subjects with normal glucose tolerance (11 males, 9 females) were evaluated in this study. Table 1 shows the results of fasting and post-glucose response of C-peptide, insulin, glucagon, GLP-1, GIP, and DPP-IV in FCPD, T2DM, and control subjects. Both the median of fasting and post-glucose C-peptide (nmol/L) in FCPD (0.07 IQR [0.05-0.21] and 0.15 IQR [0.11-0.49]) was lower than that of T2DM (0.24 IQR [0.13-0.35] and 0.94 IQR [0.43-2.19]) and the control (0.21 IQR [0.17-0.59] and 2.77 IQR [1.40-3.41]). Similarly, fasting and post-glucose insulin (mU/L) in FCPD (4.81 IQR [3.34-6.67] and 8.14 IQR [5.13-10.58]) was lower than in both T2DM (5.46 IQR

TABLE 1 Endocrine and incretin and DPP-IV response in FCPD, T2DM, and control subjects in fasting and 60 minutes after 75 g of glucose

	FCPD			T2DM			Control		
Parameter	**Fasting**	**Post-glucose**	***P***	**Fasting**	**Post-glucose**	***P***	**Fasting**	**Post-glucose**	***P***
C-peptide (nmol/L)	0.07	0.15	.090	0.24	0.94	.0004	0.21	2.77	.0004
	0.13-0.35	0.43-2.19		0.05-0.21	0.11-0.49		0.17-0.59	1.40-3.41	
Insulin (mU/L)	4.81	8.14	.025	5.46	16.19	.0012	5.70	42.54	.0012
	3.34-6.67	5.13-10.58		3.67-7.33	7.73- 7.64		4.03-8.98	20.33-63.14	
Glucagon (pmol/L)	3.44	3.44	.087	4.01	5.73	<.001	3.72	2.29	<.001
	3.34-3.74	3.34-4.01		4.01-4.30	5.44-6.02		3.44-4.01	2.01-3.15	
GLP-1 (pmol/L)	6.14	9.72	<.001	2.87	4.62	<.001	3.91	6.13	<.001
	5.55-7.99	9.00-13.14		2.05-4.11	3.21-6.19		3.30-4.63	5.16-8.44	
GIP (pmol/L)	15.8	94.14	<.001	21.85	88.29	<.001	13.00	74.65	<.001
	12.99-26.87	71.22-144.85		12.99-40.34	69.82-115.81		9.05-23.95	53.90-86.73	
DPP-IV (ng/mL)	1609.95	1995.42	.007	1204.5	1939.50	.131	1578.54	3012.0	.021
	907.42-5802.00	667.86-5802.01		679.05-2062.08	19.50-3949.5		866.71-5472.0	862.09-4617.20	

Note: All data are expressed as median with interquartile range. *P* was computed by Wilcoxon's signed rank test. Abbreviations: DPP-IV, dipeptidyl peptidase IV; FCPD, fibrocalculous pancreatic diabetes; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; T2DM, type 2 diabetes mellitus.

[3.67-7.33] and 16.19 IQR [7.73-37.64]) and the control (5.7 IQR [4.03-8.98] and 42.54 IQR [20.33-63.14]). In control subjects, in response to the glucose load, plasma glucagon (pmol/L) decreased (3.72 IQR [3.44-4.01] and 2.29 IQR [2.01-3.15]) ($P = .0006$), while it increased in T2DM (4.01 IQR [4.01-4.30] and 5.73 IQR [5.44-6.02]) ($P < .001$). In FCPD, there was no significant change in glucagon (pmol/L) (3.44 IQR [3.34-3.74] and 3.44 IQR [3.34-4.01]) ($P = .087$) in response to the glucose load.

A statistically significant difference was found between fasting and post-glucose active GLP-1 levels (pmol/L) in all groups. In FCPD, the respective fasting and post-glucose value were 6.14 (IQR [5.55-7.99]) and 9.72 (IQR [9.00-13.14]) ($P < .001$), in T2DM they were 2.87 (IQR [2.05-4.11]) and 4.62 (IQR [3.21-6.19]) ($P < .001$), and in the controls 3.91 (IQR [3.30-4.63]) and 6.13 (IQR [5.16-8.44]) ($P < .001$). Again, the median active GLP-1 (pmol/L) level was statistically significantly different in the three groups both in fasting and post-glucose test (Kruskal-Wallis test, $P < .001$ for both fasting and post-glucose state). On post hoc analysis between two groups, median GLP-1 (pmol/L) in FCPD in both fasting (6.14) and post-glucose state (9.72) was twice that of T2DM (2.87, 4.62) ($P < .001$ for both) and about 1.5 times that of the control (3.91, 6.13) ($P < .001$ for both).

The increment of GLP-1 from fasting to post-glucose state (ΔGLP-1) was also compared between the groups to rule out the possibility of high postprandial GLP-1 to be confounded by high baseline/fasting value of GLP-1. ΔGLP-1 (pmol/L) was also statistically significantly different in the three groups (Kruskal-Wallis test, $P = .001$). On post hoc analysis between two groups, ΔGLP-1 (pmol/L) in FCPD (5.3) was different from T2DM (1.39) ($P = .002$) and from the control (2.31) ($P = .023$).

Similarly, significantly higher values were found in the post-glucose state compared with the fasting values of GIP (pmol/L) in all the three groups: FCPD (15.83 and 94.14, $P < .001$), T2DM (21.85 and 88.29, $P < .001$), and controls (13.00 and 74.65, $P < .001$). But median GIP (pmol/L) in either fasting or post-glucose state was not significantly different among the three groups.

DPP-IV level (ng/mL) increased significantly after glucose load in both controls (1578.54, 3012.00; $P = .021$) and in FCPD (1609.95, 1995.42; $P = .007$). In T2DM, also DPP-IV (ng/mL) increased after glucose load, but it was not statistically significant (1204.50, 1939.50; $P = .131$). Again, there were no differences in DPP-IV levels between the three groups either in fasting or in post-glucose state.

The median value of fecal elastase (μg/g of stool) in FCPD was 8.00, in T2DM 237.67, and in the controls 501.00. In FCPD it was statistically significantly lower than in both the T2DM ($P < .001$) and control groups ($P < .001$).

Fecal elastase had a moderate correlation with increment in C-peptide ($r = 0.6$, $P < .001$) and GLP-1 levels ($r = 0.4$, $P < .001$) following a glucose challenge in the overall cohort, suggesting an endocrine-exocrine link of pancreatic function.

4 | DISCUSSION

Insulin was stopped for 24 hours and OHA for 48 hours in patients with FCPD so that insulin, C-peptide, glucagon, and incretins could be measured simultaneously. Fasting insulin and C-peptide (a surrogate for insulin secretory state) were expectedly low to very low in FCPD in comparison with T2DM and the control, and their rise in post-glucose state was also lowest in FCPD compared with the other groups. In our study, the plasma glucagon level decreased in response to oral glucose load in controls, whereas in T2DM it rose sharply, and in FCPD it did not change. This is in concordance with a previous study[9] by Mohan et al 1991, who found that plasma glucagon levels dropped down in response to oral glucose load in the control group, while they increased in T2DM. Kannan et al[14] was of the opinion that basal and stimulated glucagon levels remain higher in chronic pancreatitis, but they studied patients who were not suffering from diabetes. Similarly Keller et al showed[15] that subjects with chronic pancreatitis along with diabetes had low glucagon at basal state, but on arginine infusion the two groups showed a flat response; however, subjects suffering from chronic pancreatitis alone had a higher value.

The incretin effect, key components of which are GIP and GLP-1, is nothing but a higher insulin response to an oral glucose load as compared with intravenous glucose at similar plasma glucose levels. Recent studies have suggested a reduced postprandial GLP-1 response[16] and a diminished insulin-producing ability of GLP-1[6] as characteristic features of an impaired incretin effect in T2DM. Studies are scarce in pancreatogenic diabetes, but Knop et al[17] suggested that incretin effects were preserved in subjects with chronic pancreatitis and normal glucose tolerance, but they were reduced in those with chronic pancreatitis and diabetes.

The active GLP-1 level in our study increased significantly in post-glucose state in FCPD. It also increased significantly but at much lower amplitude in T2DM and controls. The striking finding in our study is that the active GLP-1 level was two times higher in the FCPD group compared with controls and one and a half times higher compared with T2DM both in the fasting state as well as in post-glucose state. This might be due to an exaggerated secretion of GLP-1 from the L cells in face of target organ failure analogous to negative feedback control of other endocrine systems. As GLP-1 is demonstrated to induce proliferation of pancreatic beta cells via activation of the epidermal growth factor receptor,[18] this finding might probably be related to significantly increased pancreatic malignancy in the FCPD group. However, in view of recent data, it appears to be unlikely that GLP-1 has any proliferative activity on the pancreas as evidenced from epidemiological data and recent cardiovascular outcome trials and from the fact that pancreatic carcinomas do not increase in postbariatric surgery patients in whom GLP-1 rises strikingly.

Our findings clearly elucidate that in FCPD, though included in pancreatogenic diabetes in general, the incretin response is different as compared with other causes of pancreatogenic diabetes. Our study also suggests that PERT is unlikely to cause an improvement of glycemic control in FCPD, unlike in other forms of pancreatogenic diabetes (especially chronic pancreatitis). Additionally, on the basis of our study findings, incretin-based therapies in FCPD are unwarranted.

The late-phase insulin response to GIP is diminished in T2DM as well as in pancreatogenic diabetes,[1] but comparative data on GIP levels in these groups are scarce. The GIP level in our study increased significantly in response to glucose in all groups, but increment was most robust in the FCPD group. Also, the GIP level in either fasting or post-glucose state was not significantly different among the other groups.

With the possibility that incretin levels may be different due to the differential DPP-IV enzyme level which degrades the incretins, especially in postprandial state, we assessed this enzyme level and compared it in these three groups. DPP-IV level increased significantly after glucose load in both controls and in FCPD. In T2DM also DPP-IV increased after glucose load, but it was not statistically significant. But there were no differences in DPP-IV level between the three groups in fasting state. Though the value of DPP-IV increased in all groups after glucose load, the mean DPP-IV level between the three groups was not different in post-glucose state either. This proves the fact that the robustly increased level of incretins in FCPD is primarily due to increased secretion or resistance at the effector level, but not due to preferentially more decreased levels of DPP-IV in FCPD.

Hence this study result shows that in control subjects, in response to oral glucose, plasma glucagon decreases. In T2DM, the glucagon level remains higher in basal state and increases further with glucose load. In FCPD, the glucagon level remains low in basal state, and it does not rise following glucose load. This is in concordance with the results of previous studies. Though previous studies have established that T2DM has a blunted rise in post-glucose GLP-1 levels and a diminished GLP-1 effect, recent research has confirmed that the circulating GLP-1 level is diminished in T2DM, but tissue response to GLP-1 remains intact.[19] Though we have found that active GLP-1 levels increased significantly in all groups, this increment is statistically significantly lower in T2DM compared with the control subjects ($P < .05$), a finding in consonance with the recent evidences. The median active

GLP-1 in FCPD is strikingly one and a half to two times the median value of active GLP-1 in T2DM and control subjects, both in fasting and postprandial state. In contrast, the GIP level, the other member of incretins, increases significantly in response to glucose in all groups, that is, FCPD, T2DM, and control. But the GIP level in either fasting or post-glucose state is not significantly different among the three groups. The robust increase in the incretin levels, in particular the GLP-1 level, is not likely to be explained by increment in the level of DPP-IV as such increment occurs physiologically in all groups, and we could not find any difference in this enzyme level between these three groups either in fasting state or in postprandial state. A very low fecal elastase level establishes gross exocrine pancreatic insufficiency in FCPD.

So we conclude that FCPD is a subtype of pancreatogenic diabetes, but it has some unique features which are not similar to the other forms of pancreatogenic diabetes and hence deserves special mention particularly with respect to the incretin function. Data regarding this special type of diabetes are limited, and it is a neglected area of research.[3]

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DISCLOSURE

None declared for all authors.

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