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ORIGINAL RESEARCH

Assessment of insulin sensitivity and secretion in patients with fibrocalculous pancreatic diabetes

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Background: Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes seen in patients with tropical chronic pancreatitis. Insulin deficiency plays a major role in the etiopathogenesis of FCPD. Limited data suggest a possible role of insulin resistance (IR) in the pathogenesis of FCPD. Sparse data exist on measures of insulin sensitivity (IS) and secretion in patients with FCPD and its comparison to type 2 diabetes mellitus (T2D) patients.

Method: Eighty patients with FCPD, 36 patients with T2D and 36 healthy subjects were included. A 75 g oral glucose tolerance test (OGTT) was performed in the morning after an overnight fast. We evaluated IS and secretion using indices derived from fasting (homeostasis model assessment of insulin resistance [HOMA-IR], quantitativeinsulin sensitivity check index [QUICKI] and homeostasis model assessment of beta-cell function [HOMA-ß]) and OGTT (Matsuda, insulin sensitivity index by Kanauchi [ISI-K], oral glucose insulin sensitivity index [OGIS], Stumvoll, insulinogenic index and oral disposition index [ODI]) measurements of glucose and insulin.

Results: HOMA-IR was significantly higher and QUICKI significantly lower in patients with FCPD and T2D than in healthy controls ($P<0.001$). Matsuda, ISI-K, OGIS and Stumvoll were significantly lower in patients with FCPD and T2D than in healthy controls ($P<0.001$), indicating reduced IS in both FCPD and T2D patients. HOMA-ß, insulinogenic index and ODI were significantly lower in patients with FCPD and T2D compared to healthy controls ($P<0.001$).

Conclusion: FCPD is associated with reduced IS as assessed by fasting and OGTT-based indices. FCPD is also associated with a greater degree of impairment in insulin secretion than in T2D. IR may play a role in the pathogenesis of FCPD.

Keywords: fibrocalculous pancreatic diabetes, tropical chronic pancreatitis, insulin resistance, beta-cell function, HOMA-IR, QUICKI

Introduction

Diabetes of the exocrine pancreas (DEP) is far more common than previously recognized and accounts for 1–5% of all cases of diabetes.[1,2] Chronic pancreatitis (CP) and pancreatic neoplasia are the two most common causes of DEP.[3] Tropical chronic pancreatitis (TCP) is a common cause of CP in tropical countries such as India, and the associated diabetes is termed fibrocalculous pancreatic diabetes (FCPD).[4] Although the etiology and pathophysiology of TCP are poorly understood, genetic alterations of serine protease inhibitor Kazal type 1 (SPINK1 N34S), cationic and anionic trypsinogen (PRSS1, PRSS2), oxidative stress, micronutrient deficiencies and environmental toxins have been postulated to play a role.[4–7]

The clinical presentation of FCPD encompasses a wide spectrum, ranging from impaired glucose tolerance (IGT) to overt diabetes mellitus, an insidious onset to rapid

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progression, and requiring only diet/oral medications to insulin for survival.[4,6,7] Progression to diabetes usually occurs in the second or third decade of life. As in other forms of DEP, insulin deficiency is a definitive crux. A few reports in the past two decades have suggested the possible role of insulin resistance (IR) in the glucose metabolism of FCPD.[8,9] However, the results were inconsistent on the contribution of IR to FCPD and other reports did not find IR to be a major feature of FCPD.[10,11] Small sample sizes and lack of control groups contributed to these inconsistencies and the relative importance and contribution of IR in the clinical presentation of FCPD remain unknown. The presence of IR not only is important from a pathophysiological perspective, but also has management implications as regards the potential role of medications that target IR, and may confer additional morbidity and cardiovascular risk independent of glycemic control, as in patients with type 2 diabetes (T2D).[12]

The hyperinsulinemic euglycemic clamp (HIEC) technique is considered the reference standard for estimation of insulin sensitivity (IS), but it is expensive, requires expertise, is laborious and is not suitable for epidemiological purposes. For epidemiological studies, simpler alternatives include steady-state fasting glucose and insulin-derived measures of IS, such as the homeostatic model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), and several dynamic oral glucose tolerance test (OGTT)-derived indices such as the Matsuda index (Matsuda-ISI), insulin sensitivity index by Kanauchi (ISI-K), Stumvoll index and oral glucose insulin sensitivity index (OGIS).[13–15] Both static and dynamic indices of IS have been used extensively, and, in general, shown to have good correlation with HIEC and demonstrated to be valid indicators in subjects with a wide range of glucose tolerance statuses, including those with normal glucose tolerance, obesity and IGT.[16–24] Limited data suggest that these surrogate indices of IS have good correlation with clamp-derived IS (SI_{clamp}) in patients with T2D.[24–30]

Similarly, indices for insulin secretion based on fasting parameters, such as the homeostatic model assessment of beta-cell function (HOMA-ß), and those derived from insulin responses to the OGTT, such as the insulinogenic index (IGI) and oral disposition index (ODI), have been used as markers of insulin secretion and beta-cell function in subjects with varying glucose tolerance status and diabetes.[31–36]

We hypothesized that simultaneous measurements of indices of IS and insulin secretion in patients with FCPD and their comparison with healthy non-obese controls and patients with T2D would provide a reasonably accurate assessment of the presence of IR and its relative contribution in comparison to beta-cell dysfunction. Previous studies on IS in FCPD involved different techniques and fewer subjects, and did not simultaneously assess IR and insulin secretion. Furthermore, these parameters were not studied in relation to T2D and healthy controls. Hence, we undertook this study to assess IR and insulin secretion in patients with FCPD and to compare them with T2D and healthy controls.

Research design and methods

Study design

Subjects

The present study was conducted at a tertiary care referral hospital in southern India. The study design was approved by Vydehi Institutional Ethics Committee and written informed consent was obtained from each subject. This study was carried out in accordance with the Declaration of Helsinki and US Federal Policy for the Protection of Human Subjects. The inclusion criteria were: patients with a diagnosis of FCPD or T2D, age between 18 and 65 years, Hb_{A1c} 6–12% and body mass index (BMI) <25 kg/m^2. The exclusion criteria included subjects under treatment for coronary heart disease, systemic disorders such as chronic liver disease or chronic kidney disease or endocrine disorders (except hypothyroidism), and alcohol or substance abuse.

The diagnosis of FCPD was established based on the fulfillment of all three of the following criteria:[37] 1) evidence of chronic pancreatitis: pancreatic calculi on X-ray or at least three of the following: abnormal pancreatic morphology on ultrasonography or computed tomography scan, chronic abdominal pain since childhood, steatorrhea and abnormal exocrine pancreatic function test; 2) diabetes defined according to the criteria of the American Diabetes Association; and 3) absence of other causes of chronic pancreatitis, such as autoimmune disorders, tumors, ischemia, hyperparathyroidism, pancreatic carcinoma, alcohol-related pancreatic diabetes, hypertriglyceridemia, hypercalcemia and biliary duct stone.

Initially, we recruited 80 consecutive consenting patients with FCPD between March 2017 and June 2018 attending the endocrine clinic. Subsequently, 36 patients with T2D matched for age, duration of diabetes and Hb_{A1c}, and consenting for the study were recruited. The patients with FCPD were further subgrouped into group A, with

BMI <18.5 kg/m^2 (n=37), and group B, with BMI >18.5 kg/m^2 (n=43). Twenty-one patients with FCPD were newly diagnosed; the others had been under our treatment and on enzyme replacement for at least 3 months prior to the study. Thirty-six age-matched healthy subjects without any prior history of pancreatitis or family history of diabetes, and with BMI <25 kg/m^2 and normal OGTT were recruited as controls. The controls were matched for BMI with FCPD group B. Eight subjects in our study were smokers and none of the participants in this series gave a history of habitual alcohol consumption.

Study measures

A detailed clinical history and demographic data were obtained from all the participants. Cigarette smoking status was assessed as per the National Health Interview Survey criteria and included both former and current smokers.[38] Alcohol status was assessed based on the Alcohol Use Disorders Identification Test, which includes 11 questions, and positive responses to any two questions are considered as abnormal.[39] Height, body weight and BMI were determined following the standard procedures.

OGTT

All subjects underwent a 2-hour OGTT in the morning at 08:00 h after a 12-hour overnight fast. Patients with FCPD and T2D were admitted at least 3 days prior to the study and were switched to a basal-bolus insulin regimen and titrated to maintain fasting plasma glucose (FPG) <130 mg/dL and 2-hour postprandial plasma glucose (PPG) in the range of 140–180 mg/dL. Subjects were asked to withhold oral anti-diabetic medications for 36 hours prior to the test. Long-acting and intermediate-acting insulins were withheld for 24 hours prior to the test. Hyperglycemia was corrected for 24 hours prior to the test using multiple short-acting insulin injections or insulin infusion, with blood glucose levels maintained in the range of 120–160 mg/dL. The last dose of short-acting insulin was given 8 hours prior to the study. All subjects were asked to abstain from the use of tobacco, caffeine and strong physical activity for 12 hours prior to the test. Fasting samples for blood glucose and insulin were obtained, and then 75 g of anhydrous glucose diluted in 300 mL of water was given to the patient, to be consumed over 5 minutes. Blood samples were drawn at 30, 60, 90 and 120 minutes after the ingestion of glucose for estimation of plasma glucose and serum insulin levels. About 2 mL of blood sample was drawn into fluoride Monovette tubes for glucose and 3 mL was drawn into serum separator tubes for insulin levels and cold centrifuged within 1 hour. Plasma glucose was analyzed by the hexokinase enzymatic reference method using a fully automated Beckman Coulter DXC-860i, and insulin levels were analyzed by chemiluminescence immunoassays on the same day using a Beckman Coulter DXI 600 Auto-Analyzer (Beckman Coulter, Brea, CA, USA).

Estimation of surrogate indices

Glucose and insulin areas under the curve (G_{AUC} and I_{AUC}) during the OGTT were computed using the trapezoidal method in Microsoft Excel. Surrogate indices of IS and insulin secretion were calculated according to previously published formulae[16,21,23,24,26,33,40,41] (Table 1).

Other investigations

Fasting samples for Hb_{A1c}, lipids, serum creatinine, serum calcium, serum inorganic phosphorus, serum albumin, hemoglobin and vitamin B_{12} were also collected and analyzed using a fully automated Beckman Coulter DXC-860i Auto-Analyzer (Beckman Coulter, Brea, CA, USA).

Table 1 Insulin sensitivity and beta-cell function indices derived from fasting and OGTT measurements of glucose and insulin

Index	Formula/equation
HOMA-IR	$(I_0 \times G_0)/405$
QUICKI	$1/[\log I_0 + \log G_0]$
Matsuda-ISI	$10000/\sqrt{(G_0 \times G_{mean})(I_0 \times I_{mean})}$
OGIS	Web calculator: http://webmet.pd.cnr.it/ogis/ogis.php
ISI-K	$13.192 - 0.712 \times G_0$ (mmol/L) $- 0.341 \times G_{120}$ (mmol/L) $+ 0.002 \times I_{30} - 0.003 \times I_{90}$
Stumvoll index	$[0.226 - (0.0032 \times BMI) - (0.0000645 \times I_{120}) - (0.00375 \times G_{90}$ mmol/L)]
HOMA-ß	$360 \times I_0/G_0 - 63$
IGI	$Delta[I_{30-0}$ (pmol/L)$/G_{30-0}$ (mmol/L)]
ODI	$1/I_0$ (pmol/L) $\times$ $Delta[I_{30-0}$ (pmol/L)$/G_{30-0}$ (mmol/L)]
I_{AUC}	$[I_0 + (2 * I_{30}) + (2 * I_{60}) + (2 * I_{90}) + I_{120}/4]$
G_{AUC}	$[G_0 + (2 * G_{30}) + (2 * G_{60}) + (2 * G_{90}) + G_{120}/4]$

Notes: G_0, fasting plasma glucose concentration (mg/dL); G_{30}, G_{60}, G_{90} and G_{120}, plasma glucose concentration (mg/dL) at 30, 60, 90 and 120 minutes of OGTT; G_{mean}, mean of plasma glucose concentration (mg/dL) during OGTT; I_0, fasting serum insulin concentration (mIU/L); I_{30}, I_{60}, I_{90} and I_{120}, serum insulin concentration (mIU/L) at 30, 60, 90 and 120 minutes of OGTT; I_{mean}, mean of serum insulin concentration (mIU/L) during OGTT.

Abbreviations: OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; Matsuda-ISI, insulin sensitivity index by Matsuda; OGIS, oral glucose insulin sensitivity index; ISI-K, insulin sensitivity index by Kanauchi; HOMA-ß, homeostasis model assessment of beta-cell function; IGI, insulinogenic index; ODI, oral disposition index; I_{AUC}, insulin area under the curve; G_{AUC}, glucose area under the curve.

Statistical analyses

Descriptive statistics are presented as mean ± SD for continuous variables that are normally distributed, and median (25th and 75th percentiles) for the variables that are non-normally distributed. Categorical variables are reported as count (percentage). Assessment of the assumption of normality was assessed using Q-Q plot, Kolmogorov–Smirnov and Shapiro–Wilk tests. ANOVA was used to compare the outcome measures between the groups for normally distributed variables. Pairwise comparisons between the groups for normally distributed variables were performed using Bonferroni post-hoc tests. The Kruskal–Wallis test was used to compare the outcome measures of parameters with non-normal distribution. The Mann–Whitney U-test was used for post-hoc analysis of variables with non-normal distribution. The Pearson and Spearman rank correlation tests were used to estimate the correlation between the variables. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical and biochemical characteristics of the patients in each group are presented in Table 2. The FCPD and T2D groups were matched for age, gender and duration of diabetes. In the FCPD group, six patients were on metformin, two patients on sulphonylureas, three patients on a combination of sulphonylurea and insulin, eight patients on a combination of metformin and insulin, and the rest were on insulin alone. In the T2D group, 30 patients were on metformin, 18 patients on sulphonylureas, 12 patients on DPP4 inhibitors and 15 patients were on insulin in different combinations. The mean FPG and Hb_{A1c} levels were not significantly different between the two groups. Patients with FCPD had lower BMI compared to the T2D and control groups (P<0.001). However, the BMI of FCPD Group B was not significantly different from controls and both were significantly lower than the T2D group. Serum triglyceride and low-density lipoprotein levels were significantly higher in patients with T2D compared to FCPD (P<0.001). I_{AUC} was significantly lower and G_{AUC} significantly higher in the FCPD group compared to the T2D and control groups (P<0.05). Plasma glucose and insulin responses to OGTT are presented in Figure 1.

Indices of insulin sensitivity

The comparison of insulin sensitivity indices is presented in Table 3. HOMA-IR was significantly higher in patients with T2D and FCPD compared to controls, and higher in T2D in comparison to patients with FCPD. QUICKI was significantly lower in the FCPD and T2D groups compared to controls, and higher in patients with FCPD compared to T2D (P<0.001). Matsuda-ISI was significantly lower in patients with FCPD and T2D compared to controls, and

Table 2 Baseline characteristics of the study population

	FCPD (n=80)	T2D (n=36)	Control (n=36)	P-value*
Age (years)	35.2±8.6	37.9±11.9	35.8±9.4	0.384
Male, n (%)	57(71.3%)	28(77.8%)	26(72.2%)	0.406
BMI (kg/m^2)	18.9±3.1	23.2±2.0	22.1±1.83	<0.05[ab]
Diabetes duration (years)	2.0 (0.08, 5.0)	3.0 (0.7, 5.7)	NA	0.553
FPG (mg/dL)	160 (122, 254)	175 (139, 248)	83 (78, 86)	<0.001[a]
Hb_{A1c}(%)	9.91±3.03	9.74±2.37	4.91±0.32	<0.001[a]
Total cholesterol (mg/dL)	165.4±39.5	195.5±50.5	139.7±29.9	<0.001[ab]
Triglycerides (mg/dL)	133 (88, 176)	202 (132, 297)	115 (99, 148)	<0.001[ab]
HDL (mg/dL)	41.9±9.9	38.2±8.1	39.7±7.0	0.096
LDL (mg/dL)	96.2±34.6	121.3±38.2	85.6±15.9	<0.001[ab]
Calcium (mg/dL)	9.09±0.65	9.17±0.58	8.91±0.44	0.165
Vitamin B_{12} (pg/mL)	405 (252, 722)	279 (181, 477)	429 (288, 638)	0.494
G_{AUC} (mg/dL)	628 (532, 737)	493 (433, 665)	255 (241, 283)	<0.05[ab]
I_{AUC} (mIU/L)	15.6 (8.7, 26.8)	38.2 (28.6, 45.6)	85.7 (59.1, 115)	<0.05[ab]

Notes: Data are shown as mean ± SD for normally distributed variables, or as median (25th, 75th percentiles) or n (%). *P-value using ANOVA or Kruskal–Wallis test; post-hoc analysis using Bonferroni correction/Mann–Whitney U-test; [a]FCPD and T2D are significantly different from control; [b]significant difference between FCPD and T2D groups; P<0.05 considered statistically significant.

Abbreviations: FCPD, fibrocalculous pancreatic diabetes; T2D, type 2 diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; Hb_{A1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; G_{AUC}, glucose area under the curve during OGTT; I_{AUC}, insulin area under the curve during OGTT.

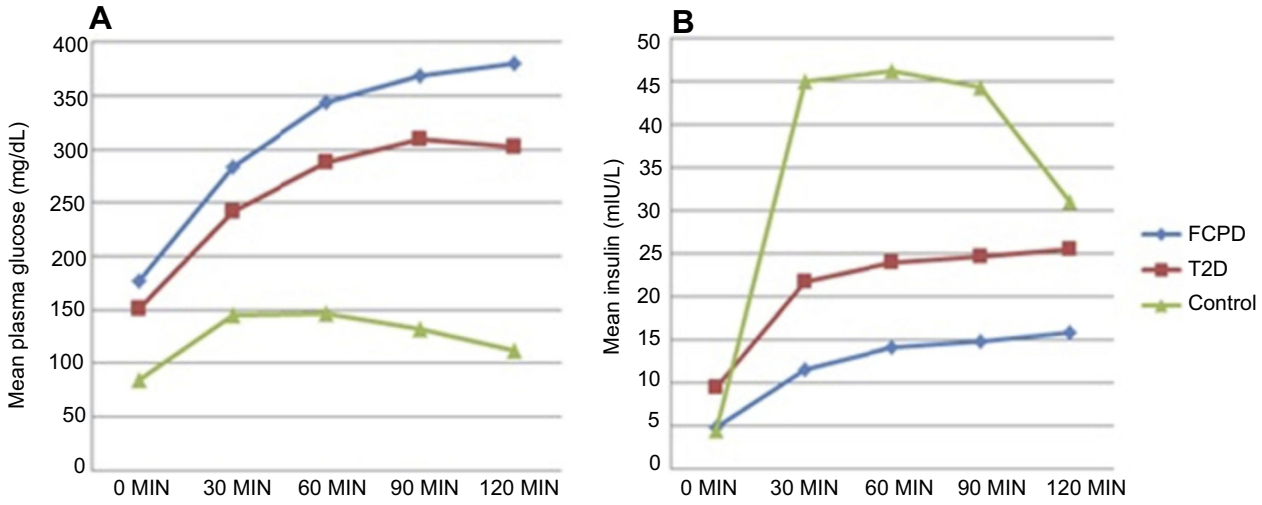

Figure 1 Plasma glucose and insulin responses during the oral glucose tolerance test. **(A)** Glucose excursion; **(B)** insulin excursion.**Abbreviations:** FCPD, fibrocalculous pancreatic diabetes; T2D, type 2 diabetes mellitus.

Table 3 Comparison of indices of insulin sensitivity between the three study groups

	FCPD	T2D	Control	*P*-value*
HOMA-IR	1.72 (0.82, 2.99)	3.03 (1.91, 4.32)	0.94 (0.63, 1.33)	<0.001[ab]
QUICKI	0.36±0.04	0.33±0.03	0.39±0.04	<0.001[ab]
Matsuda-ISI	7.80 (4.98, 13.6)	4.32 (2.67, 6.58)	8.28 (5.31, 10.9)	0.05[ab]
ISI-K	−0.75 (−4.26, 1.9)	2.63 (−0.36, 4.84)	7.69 (7.35, 7.98)	<0.001[ab]
OGIS	283 (232, 365)	328 (284, 418)	472 (430, 492)	<0.05[ab]
Stumvoll index	0.084 (0.07, 0.1)	0.086 (0.06, 0.11)	0.126 (0.12, 0.13)	<0.001[a]

Notes: Data are shown as mean ± SD for normally distributed variables, or as median (25th, 75th percentiles). **P*-value using ANOVA or Kruskal–Wallis test; post-hoc analysis using Bonferroni correction/Mann–Whitney U-test; [a]FCPD and T2D are significantly different from control; [b]significant difference between FCPD and T2D groups; *P*<0.05 considered statistically significant.

Abbreviations: FCPD, fibrocalculous pancreatic diabetes; T2D, type 2 diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance;QUICKI, quantitative insulin sensitivity check index; Matsuda-ISI,insulin sensitivity index by Matsuda; ISI-K, insulin sensitivity index by Kanauchi; OGIS, oral glucose insulin sensitivity index.

higher in patients with FCPD compared to patients with T2D. IS assessed using ISI-K was significantly lower in the FCPD and T2D groups than in the controls (*P*<0.001). OGIS also showed significantly reduced IS in patients with FCPD and T2D compared to the controls (*P*<0.001). Both ISI-K and OGIS were lower in the FCPD group compared to T2D. The Stumvoll index also showed significantly decreased IS in patients with FCPD and T2D compared to controls (*P*<0.001). The Stumvoll index was significantly lower in group B compared to group A (*P*<0.05). However, other insulin sensitivity indices were not significantly different between the two FCPD groups. Since BMI is a major determinant of Stumvoll index, an intergroup comparison was made between BMI-matched FCPD group B and controls, and it was significantly lower in group B (*P*<0.05). No significant difference was observed in the IS indices among FCPD patients with or without pancreatic enzyme replacement.

Indices of insulin secretion

The mean HOMA-ß was significantly lower in patients with FCPD and T2D compared to controls, and lower in the FCPD group in comparison to T2D (*P*<0.001). Both IGI and ODI were significantly lower in the FCPD group and T2D compared to controls (*P*<0.001). IGI was lower in the FCPD group in comparison to the T2D group. Comparisons of indices of insulin secretion are shown in Table 4. Subgroup analysis among patients with FCPD with or without pancreatic enzyme replacement revealed significantly lower IGI and ODI in the former group (*P*<0.05).

HOMA-IR and HOMA-ß showed significant positive correlation and QUICKI showed significant negative correlation with BMI in the control group (*P*<0.05) (data not shown). HOMA-IR showed significant negative correlation with age and Hb_{A1c} in patients with FCPD. QUICKI showed positive correlation with age and negative correlation with

Table 4 Comparison of indices of beta-cell function between the three study groups

	FCPD	T2D	Control	*P*-value*
HOMA-ß	12.1 (6.96, 31.4)	47.8 (23.3, 67.4)	77.0 (65.3, 111)	<0.001[ab]
IGI	3.10 (0.69, 9.42)	11.4 (4.34, 22.7)	83.8 (51.5, 155.7)	<0.001[ab]
ODI	0.17 (0.04, 0.43)	0.19 (0.07, 0.63)	2.89 (1.86, 4.79)	<0.001[a]

Notes: Data are shown as median (25th, 75th percentiles). *P-value using Kruskal–Wallis test; post-hoc analysis using Mann–Whitney U-test; [a]FCPD and T2D are significantly different from control; [b]significant difference between FCPD and T2D groups; $P<0.05$ considered statistically significant.

Abbreviations: FCPD, fibrocalculous pancreatic diabetes; T2D, type 2 diabetes mellitus; HOMA-ß, homeostasis model assessment of beta-cell function; IGI, insulinogenic index; ODI, oral disposition index.

Hb_{A1c} in patients with FCPD ($P<0.05$). No significant correlation was observed between the indices of IS and insulin secretion with other clinical parameters, including Hb_{A1c} and duration of diabetes in patients with T2D.

Discussion

We evaluated the IS and insulin secretion in a large cohort of FCPD subjects and compared them with T2D and healthy controls. The results of our study indicate reduced IS in patients with FCPD. We also found that insulin secretion was decreased to a greater extent in patients with FCPD in comparison to patients with T2D.

HOMA-IR and QUICKI are largely determined by hepatic glucose output (HGO) and are considered as reliable measures of hepatic IR both in healthy subjects and in patients with diabetes.[25,42–44] QUICKI has been shown to be significantly lower, whereas HOMA-IR is significantly higher in patients with T2D than in healthy controls.[29] Likewise, several studies demonstrated a good correlation of these indices with SI_{clamp} in subjects with T2D, although SI_{clamp} is a measure of peripheral glucose uptake (PGU).[17,19,25,27–30,45] Concerns regarding their utility in patients with T2D pertain to the fact that the linear correlation of HOMA-IR with SI_{clamp} is lost and IR is underestimated in patients with fasting hyperglycemia and significantly impaired beta-cell function. QUICKI has been shown to offer a reasonable correction in such a situation, provided its reference values are established for each laboratory for healthy controls, because of significant interlaboratory variations in insulin estimations and/or possible population-specific differences.[46,47] We recruited healthy controls for comparison and excluded patients with longer duration of diabetes to minimize this effect. Our results show that values of HOMA-IR and QUICKI in FCPD were in between those of T2D and controls. The HOMA-IR (median =1.72) clearly suggests the presence of IR in patients with FCPD compared to controls (median HOMA-IR =0.94). The results of our study are in concordance with an earlier study, which reported significantly higher HOMA-IR (>2) in 77.4% of patients with FCPD.[9] However, in a previous study, IR assessed by HOMA-IR was seen only in a minority of patients with CP.[11] In the same study, patients with CP were further classified into subgroups of alcoholic CP and tropical CP, and no significant differences were observed between the groups.

Reduced IS in the T2D group compared to FCPD using these measures could be attributed to higher BMI, higher triglyceride levels, and higher visceral and liver fat in the former group. Serum levels of triglyceride correlate with visceral fat and have been shown to be associated with IR in T2D patients.[48] However, the presence of hepatic IR in patients with FCPD with steatorrhea, lower BMI and lower triglyceride levels demands a different explanation. Three pathogenic mechanisms for hepatic IR have been proposed for patients with CP that can be extrapolated to FCPD. First, pancreatic polypeptide (PP) was shown to regulate the expression of the insulin receptor genes in the liver, and deficiency of PP due to pancreatic destruction reduced receptor expression and induced IR in experimental studies.[49] In support of this observation, reversal of hepatic IR following infusion of PP in patients with CP has also been demonstrated.[50] The second mechanism invokes impaired insulin-mediated downregulation of GLUT2 as a contributor to increased HGO in patients with CP.[51] Lastly, altered hepatic insulin action in CP has also been linked to the inflammation-based activation of hepatocyte I-κB kinase-β and nuclear factor-κB (NF-κB).[52] Blockade of NF-κB activation resulted in improved hepatic IS in rodents.[53]

Glucose and insulin excursions during OGTT can be used to derive indices of IS that exploit the hyperbolic feedback relationship between IS and beta-cell function.[54] These indices provide a reasonable estimate of IS using a minimally invasive procedure and are applicable for large-scale screening and epidemiological studies without the need for more complex and invasive protocols. Plasma glucose excursions during OGTT reflect both HGO and

PGU, as the suppression of HGO is not complete, unlike that observed with HIEC and also because some of these indices take into account both fasting and post-glucose load plasma glucose/insulin levels. This explains the lack of excellent correlation between these indices and HIEC, which estimates only PGU. All four OGTT-based indices of IS used in our study suggest reduced IS in patients with FCPD and T2D in comparison to controls. The values of Matsuda-ISI in the FCPD group were interposed between patients with T2D and controls, whereas the values of ISI-K and OGIS were lower in patients with FCPD compared to patients with T2D. These indices were chosen because of prior data in patients with T2D, including correlation with clamp studies.[24,26,30] Matsuda-ISI, a measure of whole-body IS, shows robust correlation with SI_{clamp}, is a useful tool in characterizing IR status, and has previously been shown to be lower in patients with T2D than in healthy controls.[55,56] Initially proposed as an index applicable even in advanced T2D, ISI-K was derived through multiple regression analysis of IS indices proposed by Matsuda[21], Gutt et al[57] and Stumvoll[23] et al, and estimates IS that is corrected for insulin deficiency, which is of relevance in patients with T2D in whom IR and insulin deficiency coexist. In a study conducted by Kanauchi et al, ISI-K decreased significantly with progression from IGT to T2D and showed high correlation with the HIEC (r=0.762) in T2D.[26] OGIS, which is based on a physiological model of glucose kinetics and insulin action, has shown results comparable to those of clamp, with significant correlation in subjects with T2D.[24] The values of OGIS in our study were comparable to those previously reported in T2D patients.[58] Likewise, Stumvoll yielded results comparable to those reported previously in patients with T2D.[59] In addition, when the patients were matched for BMI, the Stumvoll index was significantly lower in patients with FCPD in group B compared to T2D and controls. Since HGO and PGU contribute to a variable extent to the different OGTT-derived indices, and additional factors such as BMI determine the results of some of the indices, direct quantitative comparison of the results between FCPD and T2D is not possible.

IR has previously been demonstrated in smaller cohorts of FCPD using different techniques. Mohan et al assessed IS using an insulin tolerance test and showed that the mean glucose disposal rate was lower in FCPD compared to controls but higher than T2D.[8] Two euglycemic clamp studies conducted among patients with chronic calcifying pancreatitis and pancreatogenic diabetes found evidence of IR in CP and DEP.[60,61] In another clamp study, IR was detected in three quarters of patients with CP even in the absence of obesity.[62] In contrast, a study that used continuous infusion of glucose with model assessment (CIGMA) did not find IR in patients with FCPD.[10] The potential mechanisms underlying peripheral IR in CP and FCPD are poorly understood, although chronic inflammatory mediators may play a role. A previous study that evaluated islet cell histology in FCPD patients reported a decrease in islet cell mass as well as paucity of alpha and beta cells.[63] In contrast, histological studies involving T2D patients showed a decrease in pancreatic beta-cell volume density and an increase in alpha-cell volume density.[64] Further studies are needed to elucidate the underlying mechanisms of peripheral IR in FCPD and the differences from those implicated in T2D.

The results of our study utilizing both static and OGTT-derived indices for insulin secretion showed significantly decreased insulin secretion in patients with FCPD and T2D compared to controls. Our results also suggest more severe impairment of beta-cell function in patients with FCPD compared to patients with T2D. IGI, a measure of early-phase insulin response, has previously been shown to be lower in T2D subjects compared to healthy subjects.[36] The ODI measures the beta-cell function adjusted for insulin sensitivity and has been shown to decrease progressively from normal glucose tolerance to IFG to T2D.[33] The IGI and ODI values were significantly lower in patients with FCPD on pancreatic enzyme replacement compared to FCPD patients not on replacement. FCPD patients not on enzyme replacement represent newly diagnosed cases, and hence the relatively higher values of insulin secretion indices among them reflects relative preservation of beta-cell function in the early stage of diabetes.

The findings of our study are in concordance with previous observations in FCPD using different measures of insulin secretion. Mohan et al reported that the mean fasting C-peptide level was significantly lower in the FCPD group than in the T2D and control groups.[8] In another study, C-peptide concentrations in patients with FCPD were significantly lower than the values in healthy controls and T2D patients, but were significantly higher than those with type 1 diabetes.[65] Yajnik et al found a reduced C-peptide response to OGTT in FCPD that improved after treatment.[66] Finally, a study that assessed beta-cell function using CIGMA in patients with TCP found that beta-cell function negatively correlated with the duration of pancreatitis.[10]

The merits of this study are a relatively large sample size given the rarity of FCPD, and simultaneous assessment of insulin sensitivity and beta-cell function in comparison to T2D and healthy controls. In addition, the tests were performed under physiological conditions and define the IS and insulin secretion from a clinical standpoint. Our study findings help to further our understanding of the role of IR in the pathogenesis of FCPD. The study findings could be of importance in planning preventive strategies to reduce IR and exploring the potential role of medications that target IR.

Our study has a few limitations. The results of OGTT-based IS indices may have been potentially confounded by physiological factors such as variations in the rate of glucose absorption, incretin-stimulated insulin secretion, beta-cell function and non-insulin-mediated glucose uptake. Similarly, in patients with severe insulin secretory defect, the hyperbolic relation between IS and insulin secretion is lost and the curve is shifted leftwards and downwards.[54] This results in overestimation of IS using OGTT-based indices and may have potentially confounded our results. However, we excluded patients with longstanding diabetes to minimize this effect. Patients with FCPD had lower BMI compared to patients with T2D, and this could have biased the results of insulin sensitivity and secretion indices in FCPD group. Since the Hb_{A1c} levels were high, the impact of glucotoxicity on our findings, specifically on indices of insulin secretion, cannot be ruled out.

In summary, we showed that FCPD is associated with reduced IS, as evaluated by steady-state fasting and dynamic OGTT-based indices. FCPD was also associated with a more severe impairment of insulin secretion than in patients with T2D.

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Disclosure

The authors report no conflicts of interest in this work.

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