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The ketosis-resistance in fibro-calculous-pancreatic-diabetes. 1. Clinical observations and endocrine-metabolic measurements during oral glucose tolerance test

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Summary

We measured circulating levels of C-peptide, pancreatic glucagon, cortisol, growth hormone and metabolites (glucose, non-esterified fatty acids, glycerol and 3-hydroxybutyrate) in fibro-calculous-pancreatic diabetic (FCPD, $n = 28$), insulin-dependent diabetic (IDDM, $n = 28$) and non-diabetic control ($n = 27$) subjects during an oral glucose tolerance test. There was no difference in the two diabetic groups in age (FCPD 24 ± 2, IDDM 21 ± 2 years, mean ± SEM), BMI (FCPD 16.0 ± 0.6, IDDM 15.7 ± 0.4 kg/m^2), triceps skinfold thickness (FCPD 8 ± 1, IDDM 7 ± 1 mm), glycaemic status (fasting plasma glucose, FCPD 12.5 ± 1.5, IDDM 14.5 ± 1.2 mmol/l), fasting plasma C-peptide (FCPD 0.13 ± 0.03, IDDM 0.08 ± 0.01 nmol/l), peak plasma C-peptide during OGTT (FCPD 0.36 ± 0.10, IDDM 0.18 ± 0.03 nmol/l) and fasting plasma glucagon (FCPD 35 ± 4, IDDM 37 ± 4 ng/l). FCPD patients, however, showed lower circulating concentrations of non-esterified fatty acids (0.73 ± 0.11 mmol/l), glycerol (0.11 ± 0.02 mmol/l) and 3-hydroxybutyrate (0.15 ± 0.03 mmol/l) compared to IDDM patients (1.13 ± 0.14, 0.25 ± 0.05 and 0.29 ± 0.08 mmol/l, respectively). This could be due to enhanced sensitivity of adipose tissue lipolysis to the suppressive action of circulating insulin and possibly also to insensitivity of hepatic ketogenesis to glucagon. Our results also demonstrate preservation of α-cell function in FCPD patients when β-cell function is severely diminished, suggesting a more selective β-cell dysfunction or destruction than hitherto believed.

Key words: Fibro-calculous pancreatic diabetes; Ketosis-resistance; Oral glucose tolerance test; C-peptide; Pancreatic glucagon; Cortisol; Growth hormone; 3-Hydroxybutyrate; Non-esterified fatty acids; Glycerol

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Introduction

Diabetes in the tropics has attracted much attention in recent years. The endemic types in the tropics have been grouped in a single category as malnutrition-related diabetes mellitus (MRDM) according to a WHO study group [1]. These patients manifest peculiar metabolic features, some similar to those of insulin-dependent (type 1) diabetic patients and others to those of non-insulin-dependent (type 2) diabetic patients. Thus, the majority are insulinopenic, cachectic and dependent on exogenous insulin for control of hyperglycemia and for weight gain. However, few of them ever become ketotic despite stopping insulin treatment for long periods even when relatively large doses of insulin may be required to achieve glycaemic control. MRDM has been subdivided into two categories: (a) fibro-calculous pancreatic diabetes (FCPD) when it occurs in subjects with tropical calcific pancreatitis (TCP), and (b) protein-deficient pancreatic diabetes (PDPD) when no obvious exocrine pancreatic involvement is seen. The existence of the latter variety and indeed the role of malnutrition in the aetiology of these types of diabetes is much debated [2,3].

Numerous hypotheses have been proposed to explain the interesting metabolic feature of resistance to ketosis in MRDM. These include: (1) persistent residual β-cell function [4–9], (2) concomitant α-cell dysfunction [1,10], (3) post-meal glucagon suppression [11], (4) severely diminished body stores of fat and therefore, reduced availability of non-esterified fatty acids, the fuel for 'ketogenesis', (5) resistance of adipose tissue to lipolysis by counterregulatory hormones such as epinephrine [12,13] and (6) hepatic carnitine deficiency [14,15].

We studied plasma levels of C-peptide, pancreatic glucagon, growth hormone, cortisol, non-esterified fatty acids and the blood concentrations of 3-hydroxybutyrate and glycerol during an oral glucose tolerance test (OGTT) in patients with FCPD when first seen by us and compared them with those in IDDM patients and non-diabetic controls to establish clearly whether pathognomonic metabolic changes can be demonstrated in FCPD patients.

Subjects and Methods

A total of 83 subjects were studied. There were 28 patients with FCPD, 28 with IDDM and 27 non-diabetic controls. Details of the subjects are shown in Table 1.

FCPD was diagnosed in diabetic (WHO, 1985) individuals who gave a history of abdominal pain suggestive of pancreatitis and whose plain abdominal X-ray showed pancreatic calculi, confirmed by ultrasound. Alcohol intake was excluded by history and obstructive hepatobiliary disease by ultrasound. Fifteen patients were newly diagnosed and untreated; others had been diagnosed one month to five years previously. Of the latter, four were untreated for at least one year, two were taking glibenclamide and 7 were receiving insulin treatment (rapid acting + lente once, daily), albeit haphazardly. None of the FCPD patients showed ketonuria at presentation or during subsequent

TABLE 1

Clinical and biochemical features of subjects studied

	FCPD (28)	IDDM (28)	Controls (27)
Age (years)	21 (9–47)	21 (6–35)	27[a,b] (18–38)
Sex	M 15, F 13	M 19, F 9	M 19, F 8
BMI (kg/m^2)	16.1 (10.7–23.9)	16.2 (11.4–20.6)	21.5[a,b] (18.0–31.6)
Triceps skinfold (mm)	7 (3–16)	6 (3–13)	14[a,b] (7–35)
Plasma albumin (g/l)	35.1 (18.7–44.0)	37.9[a] (29.2–46.0)	38.0[a] (29.0–41.0)
Plasma cholesterol (mmol/l)	3.3 (1.7–5.2)	4.0[a] (2.0–5.2)	3.6 (1.8–4.7)
Plasma triglycerides (mmol/l)	1.3 (0.3–9.5)	1.0 (0.3–4.6)	0.8[a,b] (0.4–1.4)
HbA_1 (%)	11.9 (5.4–15)	14.1 (8.7–18)	6.5[a,b] (5.2–8.0)

Median (range). FCPD, fibro-calculous pancreatic diabetic; IDDM, insulin-dependent diabetic. [a] $P < 0.05$ compared to FCPD, [b] $P < 0.05$ compared to IDDM.

follow-up for up to 3 years (range 1 to 7 years), even when insulin was stopped for weeks to months (usually for socio-economic reasons) or in the presence of severe systemic infections (pyelonephritis, pulmonary tuberculosis).

IDDM patients had all shown 'significant' ketonuria at presentation (>40 mg/dl, Keto-Diastix, Ames), associated with ketoacidosis in five. Ten were newly diagnosed and untreated; 18 had been diagnosed up to 3 months before the study and were on insulin treatment (rapid acting + lente, once daily) when referred to us for investigation and management. During subsequent follow up, all showed 'significant ketonuria' or ketoacidosis either when insulin treatment was stopped for more than a few days (usually for socio-economic reasons) or during minor intercurrent infections.

Non-diabetic control subjects were less than 35 years old, without any 'pancreatic' symptoms or a first degree family history of diabetes. Plain X-ray of the abdomen and ultrasound examination were normal in IDDM and non-diabetic control subjects.

All subjects underwent a 75 g OGTT (1.75 g/kg in children below 15 years of age) after an overnight fast. Venous blood was collected in trasylol (final concentration 500 IU/ml) and plasma stored at −70°C until transported on dry ice to Newcastle-upon-Tyne, U.K. for measurement of C-peptide and to Arhus, Denmark for measurement of glucagon. Routine biochemical parameters were measured on an Abbott VP-Super autoanalyser (Irving, TX, U.S.A.) using standard kits, and glycated haemoglobin (HbA_1) by a colourimetric method using fructose standards [16]. Plasma C-peptide [17] was measured by a kit (Novo, Bagswaerd, Denmark) with a detection limit of 0.02 nmol/l and intra- and inter-batch cv <5 and <8%, respectively. Pancreatic glucagon (detection limit 5 ng/l, intra- and inter-batch cv 6 and 9.5%, respectively) was measured by wick chromatography radioimmunoassay [18] (using a specific antibody supplied by Dr. L. Heding, NOVO Research, Copenhagen, Denmark) after previous extraction in ethanol [19]. Growth hormone was measured by a double antibody radioimmunoassay using the antisera supplied free by NIH, Bethesda, U.S.A. and cortisol by a radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, U.S.A.). 3-Hydroxybutyrate and glycerol were measured on perchloric acid extracts of blood by an enzymatic assay [20] and plasma non-esterified fatty acids by an enzymatic kit (Wako Chemicals GmbH, F.R.G.).

Statistical analysis

Non-parametric statistics (Mann-Whitney U, Wilcoxon and Spearman correlations) were used for analysis. Multi-variate analysis was by multiple linear regression (MLRA) on data normalised by logarithmic transformation wherever necessary.

Results

Clinical and biochemical features (Table 1)

FCPD and IDDM patients were comparable in age, body mass index (BMI, kg/m^2) and triceps skinfold thickness; both groups were younger and thinner than control subjects ($P < 0.001$, all). Plasma albumin concentrations in FCPD patients were lower than those in IDDM patients ($P < 0.05$) as well as in control subjects ($P < 0.01$). Plasma triglyceride levels were elevated in both diabetic groups compared to control subjects, but were similar in two diabetic groups. HbA_1 concentrations were similar in FCPD and IDDM patients. All subjects showed normal plasma creatinine concentrations.

Oral glucose tolerance test

Plasma glucose (Fig. 1a) Fasting plasma glucose concentrations in FCPD patients were no different from those in IDDM patients. Plasma glucose concentrations after oral glucose were the highest in IDDM patients, being higher than those in

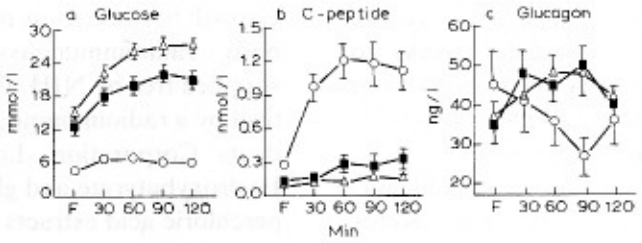

Fig. 1. Plasma glucose (a), C-peptide (b) and pancreatic glucagon (c) concentrations during an oral glucose tolerance test. Mean ± SEM. (○——○), Non-diabetic controls; (■——■), fibro-calculous-pancreatic-diabetes; (△——△), insulin-dependent (type 1) diabetes.

FCPD patients at 60, 90 and 120 min ($P < 0.05$). In FCPD patients with peak plasma C-peptide < 0.25 nmol/l during OGTT ($n = 22$), plasma glucose concentrations were higher than those in FCPD patients with peak plasma C-peptide > 0.25 nmol/l ($P < 0.05$) but not significantly different from those in IDDM patients, throughout the test.

Pancreatic islet hormones (Fig. 1b,c) β-Cell function was severely diminished in FCPD and IDDM patients compared to that in control subjects. There was no significant difference in fasting and post-glucose plasma concentrations of C-peptide between FCPD and IDDM groups; both showed a small but significant rise in plasma C-peptide concentrations after oral glucose ($P < 0.001$, compared to basal). Plasma C-peptide response to oral glucose showed a spectrum in FCPD, but peak plasma C-peptide was < 0.25 nmol/l in 22 patients, emphasizing the severity of insulinopenia.

Fasting plasma glucagon concentrations were similar in the three groups of subjects studied. After oral glucose both FCPD and IDDM patients showed a 'paradoxical' rise in glucagon concentrations, and there was no significant difference between the two at any time. Control subjects showed a significant fall in plasma glucagon concentrations 90 min after oral glucose ($P < 0.05$). Plasma glucagon concentrations were higher in both diabetic groups than those in controls at 60 and 90 min ($P < 0.05$, all) after oral glucose.

Other hormones (Table 2) Plasma levels of growth hormone and cortisol were available in 21 FCPD, 16 IDDM and 10 control subjects. Both FCPD and IDDM patients showed elevated fasting concentrations of growth hormone compared to control subjects ($P < 0.01$, both); there was no significant difference between the diabetic patients. After oral glucose, plasma growth hormone concentrations showed a transient fall in FCPD at 60 min ($P < 0.05$), it remained unchanged in IDDM patients. Plasma

TABLE 2

Plasma growth hormone and cortisol concentrations during OGTT

	FCPD	IDDM	Controls
Growth hormone (ng/ml)			
fasting	3.4	4.8	0.7[a, b]
	(0.1–22.5)	(0.2–15.8)	(0.1–5.3)
1 h	0.91[c]	2.70	0.30[a, b]
	(0.10–8.10)	(0.60–13.70)	(0.10–1.20)
2 h	3.1	3.3	0.2[a, b]
	(0.1–18.4)	(1.0–7.5)	(0.1–1.5)
Cortisol (μg/dl)			
fasting	11.4	15.8	13.8
	(7.6–24.8)	(11.2–45.7)	(3.5–17.7)
1 h	7.1	11.4	13.8
	(5.4–19.1)	(6.3–27.1)	(11.7–25.4)
2 h	9.3	13.6	12.6
	(6.3–21.3)	(7.1–24.2)	(4.2–22.3)

Median (range). FCPD, fibro-calculous pancreatic diabetic; IDDM, insulin-dependent diabetic. [a] $P < 0.05$ for difference from FCPD; [b] $P < 0.05$ for difference from IDDM; [c] $P < 0.05$ for difference from fasting value for the same group.

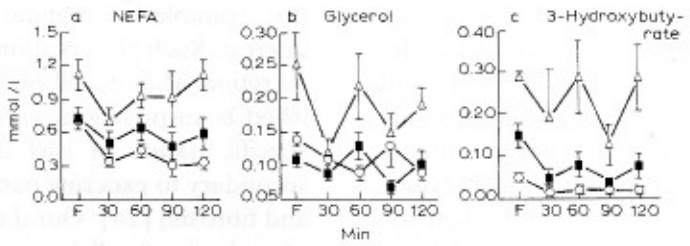

Fig. 2. Plasma non-esterified fatty acids (a), blood glycerol (b) and 3-hydroxybutyrate (c) concentrations during an oral glucose tolerance test. Mean ± SEM. Key as in Fig. 1.

cortisol concentrations were similar in all three groups and did not show any significant change after oral glucose.

Metabolites (Fig. 2) In FCPD patients, fasting concentrations of plasma non-esterified fatty acids and blood glycerol as well as 3-hydroxybutyrate were lower than those in IDDM patients ($P < 0.05$, all). After oral glucose, there was a significant fall in concentrations of non-esterified fatty acids (60 min, $P < 0.05$), glycerol and 3-hydroxybutyrate (90 min, $P < 0.05$, both) in FCPD patients but not in IDDM patients. Blood-3-hydroxybutyrate concentrations after oral glucose remained persistently higher in IDDM patients than in FCPD patients ($P < 0.01$).

There was a direct correlation between non-esterified fatty acid and 3-hydroxybutyrate concentrations in FCPD patients ($r_s = 0.47$, $P < 0.05$), but not in other groups. Fasting concentrations and the fall after oral glucose of these metabolites were unrelated to BMI, plasma glucose, C-peptide or glucagon concentrations.

Multivariate analysis

Multivariate analysis revealed that in fibrocalculous pancreatic diabetic patients, 3-hydroxybutyrate and non-esterified fatty acid concentrations were both significantly related to plasma triglyceride concentrations ($P < 0.01$) allowing for age, BMI, plasma glucose, plasma C-peptide and glucagon concentrations. In insulin-dependent diabetic patients, non-esterified fatty acid concentrations were related inversely to age and directly to BMI and fasting glucose concentrations ($P < 0.05$, all); and 3-hydroxybutyrate concentrations to plasma triglyceride concentrations ($P < 0.05$).

Discussion

Our clinical follow-up of FCPD patients over the last 7 years suggests that FCPD patients could be called 'ketosis-resistant'. None showed ketonuria at presentation despite severe hyperglycaemia, substantial weight loss and a long duration of diabetic symptoms (up to 5 years). Also, during subsequent follow-up, none of the patients who had stopped insulin for many weeks nor those who suffered severe systemic infections developed ketosis. It is possible that some of the FCPD patients develop severe ketoacidosis in remote places and die without proper diagnosis and treatment and will be excluded from hospital based study like ours. However, many of our IDDM patients also came from similar socioeconomic and rural backgrounds but showed significant ketosis at presentation or during subsequent follow-up.

Blood levels of metabolites paralleled the clinical behaviour. Thus, fasting concentrations of 3-hydroxybutyrate as well as non-esterified fatty acids and glycerol were higher in IDDM patients compared to FCPD patients. A carry over effect of the previous day's insulin injection is possible but would be biased in favour of IDDM patients because a larger number were receiving insulin treatment. Plasma glucose concentrations were comparable in the two groups, as were plasma

concentrations of C-peptide and glucagon, suggesting comparable β- and α-cell function under the conditions of the study. Similar BMI and triceps skinfold thickness in the two groups suggest comparable energy nutrition and subcutaneous fat stores. Thus, a majority of previous explanations for the contrast between ketosis-resistant behaviour of FCPD patients and ketosis-proneness of IDDM patients seem inadequate in our patients.

It has been shown previously that ketosis-resistant FCPD patients possessed better β-cell function than those who had developed ketosis [5], and it has been suggested that residual β-cell function is the major factor in ketosis-resistance of these patients [21]. However, more than 75% of our FCPD patients (most newly detected) who showed very low C-peptide reserve were also 'ketosis-resistant'. Their β-cell function was no different than ketosis-prone IDDM patients. This implies that residual β-cell function could not be the sole explanation for their metabolic behaviour. We have shown improvement in β-cell function of FCPD patients after treatment [22]. Such an improvement in treated patients could protect them further against the development of ketosis in adverse conditions.

'Normal' plasma glucagon concentrations in the FCPD group were unexpected in the light of previous assertions [1]. Mohan et al. [10] showed normal fasting plasma glucagon concentrations in their FCPD patients which did not change after oral glucose. Subjects in that study were however, selected for substantial residual β-cell function and as such do not represent the majority of FCPD patients who are insulinopenic. Our results show that the α-cell function in our FCPD patients was preserved even when β-cell function was severely diminished (associated with severe exocrine pancreatic loss after years of chronic pancreatitis [23]). Indeed, it was no different from that of comparable IDDM patients, including the 'paradoxical' rise after oral glucose. Glucagon deficiency could not therefore, be a major explanation for ketosis-resistance in our FCPD patients. More formal testing of α-cell 'reserve' (for example by arginine infusion) would be of interest. Such preservation of pancreatic glucagon secretion when β-cell function is severely diminished is surprising in view of the expected non-specific nature of islet damage in FCPD, i.e. secondary to exocrine pancreatitis (inflammation and fibrosis) [24]. Our data raises the possibility of a selective β-cell damage or the surviving α-cells appear to compensate adequately.

The ketosis-resistance in severely insulinopenic and hyperglycaemic FCPD patients is thus not fully explained. Plasma concentrations of growth hormone and cortisol were also comparable to those in IDDM patients. Lower concentrations of lipolysis products (non-esterified fatty acids and glycerol) in FCPD patients compared to those in IDDM patients could argue for better suppression of adipose tissue lipolysis by the circulating insulin in FCPD, alternatively an unmeasured inhibitor of lipolysis (i.e., IGF) could be responsible. Previous studies [12,13] have shown in vivo as well as in vitro resistance to catecholamine induced lipolysis in 'ketosis-resistant young diabetic' (KRYD) patients from North India. The relationship of those patients to FCPD is, however, not clear.

In addition to the enhanced insulin sensitivity of the adipose tissue, FCPD patients could also have a degree of glucagon-insensitivity of hepatic ketogenesis, because the concentrations of non-esterified fatty acids were comparable to normal controls (Fig. 2) and hepatic ketogenesis is expected to be stimulated when the glucagon-insulin ratio is high [25]. Carnitine deficiency from a lysine-limited cereal-based diet [14] could be responsible.

In summary, we have shown that the previous explanations for ketosis-resistant behaviour of FCPD patients are inadequate. Severely insulinopenic FCPD patients with 'normal' plasma glucagon and non-esterified fatty acid concentrations were also ketosis-resistant. It would appear that small concentrations of circulating insulin in these patients are able to suppress lipolysis more effectively than in comparable IDDM patients. Hepatic ketogenesis could also be insensitive to

the influence of glucagon. The metabolic basis for these observations, including the role of carnitine deficiency deserves further investigation. Moreover, 'normal' plasma glucagon concentrations when C-peptide concentrations are severely diminished raises the possibility of a selective β-cell damage in FCPD.

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