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Suppression of Free Fatty Acids by Oral Glucose in Patients with Cystic Fibrosis

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Abstract

Aim: The oral glucose tolerance test (OGTT) is part of the routine management and readily detects impaired insulin secretion in the majority of adult patients with cystic fibrosis (CF). To assess an activity of endogeneous insulin on adipose tissue in these patients, we analyzed serum levels of insulin and free fatty acids (FFA) in response to oral glucose since glucose-induced insulin decreases FFA and thus, suppression of FFA reflects an insulin effect on adipose tissue.

Methods: Adult patients with end-stage CF lung disease without known dysglycemic disorder and a control group of healthy subjects were included. We assessed levels of two adipokines, adiponectin and leptin, and suppression of FFA during OGTT. Insulin secretion was estimated by the insulinogenic index (IGI), and whole body and adipose tissue insulin sensitivity by the indices ISI comp and ISI fat, respectively.

Results: OGTTs were performed in 39 patients and 23 controls. Plasma glucose at 2h was higher and IGI was lower in patients with CF than in controls. ISI comp and ISI fat were similar in patients with CF and in controls. During OGTT, FFA decreased to a comparable extent in both groups. Leptin was lower whereas total adiponectin tended to be higher and its HMW form was significantly higher in patients with CF than in controls.

Conclusion: Residual insulin (in face of apparently normal insulin sensitivity and increased energy expenditure and – possibly adiponectin-enhanced – FFA oxidation) appears to be sufficient for maintaining FFA homeostasis in patients with advanced CF lung disease.

Keywords
Oral glucose tolerance test, Cystic fibrosis related diabetes, Insulin sensitivity, Free fatty acids, Adiponectin, Leptin

Abbreviations
A1c: Glycated Haemoglobin; AUC: Area Under Curve; CF: Cystic Fibrosis; CFRD: Cystic Fibrosis Related Diabetes; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; FEV1: Forced Expiratory Volume in 1 Second; GH: Growth Hormone; h: Hours; HMW: High Molecular Weight; IGF-1: Insulin-Like Growth Factor-1; IGI: Insulinogenic Index; IGT: Impaired Glucose Tolerance; INDET: Indeterminate Glucose Tolerance; IQR: Interquartile Range; ISI comp: Whole Body Insulin Sensitivity Index; ISI fat: Adipose Tissue Insulin Sensitivity Index; NGT: Normal Glucose Tolerance; OGT: Oral Glucose Tolerance; OGTT: Oral Glucose Tolerance Test; PG: Plasma Glucose U/V: Unit/Volume

Introduction
Cystic fibrosis (CF) is a multi-organ disease, characterized by chronic systemic inflammation and high-energy expenditure. Exocrine pancreatic insufficiency often develops in the first year of life. Malnutrition and low body weight are common clinical findings in CF despite enzyme replacement therapy. Endocrine pancreas insufficiency appears later in course of disease. However, improved symptomatic treatment regimens and better outcomes following lung transplantation have contributed to an improved overall life expectancy in patients with CF over the last years [1]; Thus, disorders of glucose homeostasis increasingly emerge in clinical practice.

Up to half of adult patients with CF have CF related diabetes (CFRD). CFRD is related to increasing age, duration of exocrine pancreatic failure, and the Phe508del homozygous state. In
addition, oral glucose tolerance test (OGTT) detects impaired glucose tolerance (IGT; Fasting, ≤ 7.0 mmol/l and 2h plasma glucose (2hPG), ≥ 7.8 mmol/l and ≤ 11.0 mmol/l) or indeterminate glucose tolerance (INDEXED; fasting, ≤ 7.0 mmol/l and 2hPG, ≤ 7.7 mmol/l, but 1hPG ≥ 11.1 mmol/l) in another substantial proportion of patients [2,3]. At our centre, the majority of patients (75%) are diagnosed with CFRD at the time of evaluation and listing for lung transplantation [4]. Inflammatory pancreatic tissue destruction and subsequent islet cell loss is probably a main cause of CFRD and impaired glucose tolerance [5,6]. While the decreased insulin secretion is well accepted in the pathogenesis of CFRD, the role of insulin resistance is less clear, and data are conflicting [6].

Patients with CFRD rarely present with ketoacidosis, suggesting that a complete lack of insulin action is rather exceptional in patients with CF. Adipose tissue is often reduced in patients with CF, and clearance of energy-providing substrates such as glucose and FFA is high even if ambient insulin concentrations are relatively low, i.e. non-insulin-mediated glucose and FFA disposal may be increased. Patients with CF have increased resting energy expenditure, related to the CF transmembrane conductance regulator (CFTR) gene, pancreatic and lung function, and inflammatory and nutritional status [7,8]. FFA release from stored triglycerides (lipolysis) is very sensitive to suppression by insulin, and in most conditions, insulin appears to control FFA levels by reducing their endogenous appearance rate [9]. Epidemiological studies have linked increased FFA levels to obesity, insulin resistance, and type-2 diabetes. The adipose tissue insulin sensitivity index as proposed by Belfiore (ISIw) is based on suppression of FFA in an OGTT by endogenous insulin; and the ISIw was decreased in such patients [10,11]. However, studies applying this method in patients with CF are lacking.

Adiponectin is by far the most abundant adipokine, it has anti-inflammatory and insulin-sensitizing properties. It circulates in several forms; the most abundant are high molecular-weight (HMW) multimers. In patients with obesity, insulin resistance, hyperinsulinemia, and type 2 diabetes, the levels of adiponectin and specifically its HMW form are reduced [12,13]. Adiponectin is elevated in patients with type 1 diabetes and in patients with anorexia nervosa [14-16].

Leptin is predominantly secreted from adipocytes; its serum levels usually correlate positively with fat mass and body weight. Therefore, elevated serum leptin levels are common in obesity and possibly thereby associated with insulin resistance and hyperinsulinemia. In contrast, anorectic and underweight patients show low leptin levels [15].

The main goal of our study was to assess suppression of FFA during OGTT; moreover, we measured adiponectin and leptin in patients with CF evaluated for lung transplantation.

Methods

Subjects

Over a 10-year period, we recruited consecutive patients with CF undergoing evaluation for lung transplantation. Inclusion criteria were age ≥ 18 years and agreement to participate in the study. Exclusion criteria were known previous fasting PG ≥ 7 mmol/l, insulin treatment, corticosteroid therapy and BMI ≥ 30 kg/m². We used control subjects who had an OGTT for other reasons (i.e., diagnostic evaluation of a potential hypoglycemic disorder, or exclusion of acromegaly) and in whom a dysglycemic disorder was excluded [17]. Study patients and controls were matched for age and gender. The study was approved by the Local Ethics Committee and written informed consent was obtained.

CF status

All patients with CF undergoing evaluation for lung transplantation had forced expiratory volume in 1 second (FEV₁) measured by spirometry and their body weight by an electronic scale. All data were collected within 1 week of OGTT. CF genotype status was retrieved from patients’ records.

Laboratory values and oral glucose tolerance test

All patients and the control group had laboratory analysis as described below and underwent a standard 75 g OGTT. In the morning after an overnight fast, a peripheral intravenous line was placed into the antecubital vein of all subjects followed by the ingestion a solution with 75 g glucose. Blood samples for glucose, insulin and FFA were obtained at baseline (mean of two samples, taken 15 min and immediately before) as well as 30, 60, 90, and 120 min after glucose load. According to the results of the OGTT, study patients were divided in two groups: one group with CFRD and the other without CFRD. CFRD was diagnosed when glucose readings 120 minutes after glucose load were ≥ 11.1 mmol/l.

Laboratory measurements

Venous PG was measured by the hexokinase method (Beckman Analyzer; Fullerton, CA, USA), serum insulin by solid phase radioimmunoassay (CIS Bio International, Oris Industries, Gif-Sur-Yvette, France) and FFA by an enzymatic endpoint calorimetric assay (Wako Diagnostics, 1600 Bellwood Road, Richond, VA 23237-1326, USA). Glycated Haemoglobin (A1c) was measured by immunoturbidimetric method in EDTA blood samples. Adiponectin was measured by EIA (R&D Systems, Inc., 614 McKinley Place NE, Minneapolis, MN 55413) and its high molecular weight (HMW) multimer form by ELISA (ALPCO, 26-G Keewaydin Drive, Salem, NH 03079). Leptin was measured by Human Leptin ELISA Kit (Cat. EZHL-80SK, EMD Millipore Corporation, St. Charles, Missouri 63304 USA).

β-cell function and insulin sensitivity indices

To estimate β-cell function, the insulinogenic index (IGI) was calculated as proposed by Wareham, i.e., as the ratio of the increment of serum insulin (between 0 and 30 min) to PG at 30 min after the glucose load [18]. Whole body insulin sensitivity index (ISI_comp) was calculated by data obtained during the OGTT according to Matsuda and DeFronzo: ISI_comp = 10,000/square root of [(mean plasma insulin × mean glucose during OGTT) × (fasting PG × fasting plasma insulin)]. Insulin sensitivity of adipose tissue (ISIw) was estimated as proposed by Belfiore [10]: ISIw = [((area under curve (AUC) 0→30 min × AUC 30→120 min)+1], where AUC 0→30 min and AUC 30→120 min represent insulinemic and FFA areas under curve (AUC) during
OGTT of the person under study divided by the mean inuline- or FFA AUC of control group. AUC was calculated as unit/volume \((U/V) \times \min^{-1} = [(U/V_0' + U/V_{30'}) \times 30/2] + [(U/V_{30'} + U/V_{60'}) \times 30/2] + [(U/V_{60'} + U/V_{90'}) \times 30/2] + [(U/V_{90'} + U/V_{120'}) \times 30/2].

Statistics

Data are presented as median and interquartile range (IQR) since some of the values were not normally distributed. Accordingly, the statistical evaluation for potential differences between the groups of patients and controls was done by unpaired Wilcoxon rank-sum test. \(p < 0.05\) was considered significant.

Results

Characteristics of patients with CF

Data are shown in Table 1. Thirty nine patients with CF (21 women; median age 24 (IQR 21-35) y) and 23 controls (12 women; median age 31 (IQR 23-35) y) were included in the study. Nineteen patients were homozygous and 14 were heterozygous for Phe508del, respectively; six patients had other CF-defining genotypes. The CF-group was fairly homogenous.

Table 1: Characteristics of patients with CF and controls.

|                           | Controls | CF total | CF no CFRD | CF CFRD |
|---------------------------|----------|----------|------------|---------|
| Number (n)                | 23       | 39       | 25         | 14      |
| Men/Women (n)             | 11/12    | 18/21    | 13/12      | 5/9     |
| Age (y)                   | 31 (23; 35) | 24 (21; 35) | 23 (21; 34) | 26 (23; 38) |
| CFTR genotype\(^*\)       | 0/0/0/0/23 | 19/14/6/0 | 12/8/5/0  | 7/6/1/0 |
| BMI (kg/m\(^2\))          | 22.0 (20.7; 24.8) | 18.0 (16.8; 19.7) | 18.4 (17.2; 19.8) | 17.8 (15.5; 19.8) |
| FEV1 (%)                  | not analyzed | 28 (21; 38) | 32 (26; 46) | 23 (19; 31) |
| A1c (%)\(^1\)            | 5.4 (5.3; 5.6) | 6.1 (5.9; 6.3) | 6.0 (5.8; 6.2) | 6.2 (6.0; 6.6) |
| A1c (mmol/mol)\(^1\)      | 36 (34; 38) | 43 (41; 45) | 42 (40; 44) | 44 (42; 49) |
| Glu0’ (mmol/l)            | 4.5 (4.2; 4.7) | 4.7 (4.5; 5.3) | 4.6 (4.5; 5.1) | 5.2 (4.6; 5.9) |
| Albumin (g/l)\(^2\)       | 41 (39; 45) | 38 (35; 41) | 38 (35; 41) | 38 (35; 40) |
| CRP (mg/l)\(^3\)          | 0 (0; 2) | 11 (5; 30) | 12 (5; 38) | 7 (4; 22) |

Data are expressed as median (IQR).

\(^*\)Phe508del homozygous/heterozygous/other genotype/not analysed.

\(^{1}\): Measured in 13 of 23 controls; \(^{2}\): Measured in 19 of 23 controls and 38 of 39 CF patients; \(^{3}\): Measured in 21 of 23 controls.

Table 2: Adiponectin and leptin; Glucose, insulin and free fatty acids during OGTT and derived indices.

|                            | Controls | CF total | CF no CFRD | CF CFRD |
|---------------------------|----------|----------|------------|---------|
| Leptin (ng/ml)            | 6.1 (2.8; 12.8) | 1.9 (0.5; 3.6) | 1.2 (0.6; 3.2) | 2.1 (0.5; 7.2) |
| Adiponectin (μg/ml)        | 7.4 (4.8; 11.9) | 9.4 (8.1; 12.6) | 9.1 (7.2; 12.3) | 11.1 (9.0; 12.9) |
| HMW adiponectin (%)\(^1\)  | 40 (27; 44) | 52 (46; 58) | 48 (45; 54) | 58 (50; 62) |
| Glu0’ (mmol/l)            | 4.5 (4.2; 4.7) | 4.7 (4.5; 5.3) | 4.6 (4.5; 5.1) | 5.2 (4.6; 5.9) |
| Glu120’ (mmol/l)          | 5.7 (4.4; 7.0) | 9.4 (7.0; 13.0) | 7.6 (4.8; 9.2) | 14.0 (13.0; 16.0) |
| AUC glu (mmol/l × 120 min) | 797 (762; 890) | 1188 (936; 1302) | 995 (849; 1172) | 1412 (1264; 1651) |
| Ins0’ (pmol/l)            | 100 (82; 136) | 107 (79; 129) | 109 (81; 129) | 86 (57; 149) |
| Ins120’ (pmol/l)          | 377 (206; 646) | 349 (276; 632) | 343 (234; 658) | 434 (296; 612) |
| AUC ins (pmol/l × 120 min) | 57060 (42450; 69105) | 38340 (31560; 56295) | 48990 (36270; 64905) | 31680 (22283; 36780) |
| FFA0’ (mmol/l)            | 0.63 (0.29; 0.97) | 0.53 (0.35; 0.81) | 0.49 (0.33; 0.65) | 0.77 (0.42; 1.00) |
| FFA120’ (mmol/l)          | 0.09 (0.05; 0.20) | 0.13 (0.05; 0.19) | 0.13 (0.07; 0.18) | 0.14 (0.04; 0.20) |
| AUC FFA (mmol/l × 120 min) | 29.7 (11.9; 50.3) | 31.7 (20.1; 42.0) | 23.9 (19.5; 36.5) | 37.4 (28.1; 53.1) |
| IGI\(_{\text{pH}3.0/25^\circ}\) (pM/mM) | 58.3 (46.9; 81.3) | 14.5 (7.4; 27.7) | 21.4 (14.2; 31.0) | 7.3 (4.8; 10.2) |
| ISI\(_{\text{comp}}\) (1/mMpM) | 9.2 (7.0; 11.0) | 8.5 (6.4; 11.4) | 8.0 (6.7; 10.5) | 9.3 (5.7; 12.0) |
| ISI\(_{\text{fat}}\) (index) | 1.20 (0.80; 1.50) | 1.20 (1.10; 1.40) | 1.20 (1.05; 1.45) | 1.25 (1.08; 1.35) |

Data are presented as median (IQR).

\(^{1}\): measured in 15 of 23 controls and 35 of 39 CF patients.
as all patients were undergoing lung transplantation assessment, implicating that all of them were suffering from severe lung disease, dominating their markedly reduced health status. Their median FEV₁ was 28 (IQR 21-38)%. BMI was significantly lower, fasting PG was borderline and A1c on average markedly higher, albumin was lower and CRP higher in patients with CF than in controls.

Plasma glucose during OGTT

Data are shown in Table 2 and Figure 1. Fasting PG was similar in patients without CFRD and controls and slightly higher in patients with CFRD. PG 2 hours after glucose intake was much higher in patients with CF than in controls. Compared to control group, the 2hPG was only slightly increased (p < 0.05) in patients without CFRD and much higher (p < 0.0001) in those with CFRD (by definition, ≥ 11.1 mmol/l). A new diagnosis of CFRD was made in 14 (36%) patients. In addition, 10 (26%) patients with CF had IGT, and 4 (10%) INDET (both subgroups included in the 25 CF no CFRD in Table 1 and Figure 1).

Insulin, OGTT-derived indices and FFA suppression

Data are shown in Table 2 and Figure 1. Insulin measured before and 2 hours after glucose intake was similar in patients with CF and controls. However, in patients with CF the insulin peak was delayed, leading to a significantly lower IGI in patients with CF compared to controls. The decrease in IGI was more pronounced in patients with CFRD, and less marked (intermediate) in those with IGT and INDET. Of note, patients without CFRD but especially those with IGT or INDET also showed delayed insulin secretion with a peak after 90 minutes, having a low IGI but normal AUC of insulin. In contrast to the significantly decreased IGI in CF patients, ISI_comp and ISI_fat were similar in patients in controls and CF-patients (and independent whether CFRD was diagnosed or not). Despite lower and delayed insulin secretion (resulting in higher glucose values) in patients with CF, FFA decreased to a similar extent as in controls, irrespectively of whether subjects had CFRD or not.

Adiponectin and Leptin

Data are shown in Table 2 and Figure 2. Total adiponectin was similar in patients with CF and controls (with a trend for higher values in the former group), and HMW-adiponectin was significantly higher in patients with CF than in controls. Leptin was significantly lower in patients with CF than in controls.

Discussion

Our results confirm previous reports on high diabetes incidence in patients with CF, and the low IGI is in line with the generally accepted view of impaired insulin secretion as an important pathogenic mechanism in CFRD. Nevertheless, oral glucose suppressed FFA to a similar extent in patients with CF compared to controls.

Patients with type 2 diabetes have impaired insulin-mediated FFA suppression by OGTT, and therefore, a low ISI_ia [10]. Carlson, et al. reported on a small subgroup of elderly patients with isolated post challenge hyperglycemia (i.e., normal fasting and diabetic 2hPG values), similar to the majority of our CF patients. This subgroup was characterized by increased FFA levels (basal and during OGTT), despite increased insulin levels at 2h [19]. The authors concluded that elevated FFA not only reflect but also contribute to insulin resistance and elevated 2hPG levels. Although not consistently insulin resistant as most obese patients with type 2 diabetes, fluctuating insulin sensitivity contributes to changes in glucose tolerance of patients with CF and normal glucose tolerance (NGT), INDET or IGT; this may well account for the characteristically high variability in oral glucose tolerance (OGT) in patients with CF [2,20,21]. It is conceivable that in patients with a given reduced insulin secretion and
uptake. ISIcomp calculated by data obtained during OGTTs
skeletal muscle is the main target for high rates of glucose
be found by hyperinsulinemic glucose clamp studies where
the context of inflammation and low muscle mass; it may
healthy individuals. Insulin resistance is to be expected in
resistance, OGT may rapidly change over time, more than in
patients with type1 diabetes [16], but whether the same is true
-ance rates correlate with adiponectin in controls and in pa-
sensitivity. At low insulin concentrations, glucose disappear-
theses FFA oxidation [28] and may enhance clearance of FFA.
according to studies in animals, adiponectin acts in the brain
downregulate adiponectin in patients with anorexia and in
High adiponectinemia has been shown to be associated with
HMW-adiponectin is often increased in severely ill patients.
Enlarged adiponectin levels have been found in some [24,25],
but not all [26] studies, possibly related to inflammation,
chronic energy deficit and wasting. According to our results,
HMW-adiponectin is often increased in severely ill patients.
Hyperadiponectinemia has been shown to be associated with
underweight and malnutrition and normalizes after refeed-
particularly HMW-adiponectin is increased in patients
with anorexia [15]. It remains unclear whether insulin can
downregulate adiponectin in patients with anorexia and in
patients with CF. Furthermore, it is unknown whether high
adiponectin levels contribute to or merely reflect wasting.
According to studies in animals, adiponectin acts in the brain
to increase energy expenditure [27], and adiponectin stimu-
lates FFA oxidation [28] and may enhance clearance of FFA.
This may contribute to normal FFA levels in patients with CF
and insulin deficiency. Although not directly estimated in our
study subjects, increased resting energy expenditure in our
patients with CF is likely. Given that adiponectin increases
insulin sensitivity by stimulating FFA oxidation, the high ad-
iponectin could explain the “unexpectedly” normal insulin
sensitivity. At low insulin concentrations, glucose disappear-
ance rates correlate with adiponectin in controls and in pa-
tients with type1 diabetes [16], but whether the same is true
for glucose and FFA disappearance in patients with CF has not
yet been specifically studied.

Distinct patient and control populations most likely ex-
plain different findings regarding adiponectin in CF studies,
moreover, interfering drug treatment and differences in methodology. All of our patients had end-stage CF lung disease (so that they were probably not ideal to check for a possible relation between disease severity and adiponectin elevation). They were matched with controls for age but not for BMI, also characteristically having lower albumin and higher CRP levels than the controls; they did not receive corticosteroid or insulin treatment.

Similar to our results, Cohen, et al. [29] found decreased levels of leptin in adult patients with advanced CF. Their patients with severe CF were also not weight-matched to controls, and fat mass was closely related to leptin, suggesting that decreased leptin levels were more likely a consequence than a cause of weight loss. Ziai, et al. [30] found comparable leptin levels between CF patients and BMI-matched controls, demonstrating correlations between insulin and leptin levels after adjusting for gender and fat mass. Insulin increases plasma leptin concentrations in normal subjects and patients with type-2 diabetes [31] but corresponding studies have not been performed in patients with CF.

Limitations of our study include the extended observation period and single-center design, our heterogeneous, incompletely matched control group, and the lack of body composition and energy expenditure data. On the other hand, our study cohort was homogenous regarding the stages of their CF lung disease.

The impact of given insulin concentrations on the regulation of PG, or estimated appearance and disappearance rates of glucose from and into target tissues (liver and muscle) define the terms insulin sensitivity and resistance. Yet, insulin has additional important effects such as inhibition of lipolysis and proteolysis. Adipose tissue is not a dominant tissue for overall glucose disposal, nevertheless, is an important target tissue of insulin action. FFA suppression and ISI_s have been used to estimate insulin sensitivity and resistance of adipose tissue to actions of insulin [10], although insulin is not the only determinant for FFA (as for glucose) appearance and disappearance rates. In patients with CF, increased GH could favour lipolysis, and low insulin attenuate its most important brakes.

Most often, however, production and release of energy-providing substrates appear to remain well matched to increasing demands in patients with CF (at the expense of body mass, unless met by appropriate nutrition). Beyond the control of glucose and FFA levels, insulinopenia in these patients is especially deleterious for protein metabolism and skeletal muscle in these patients [4,32]. Food-induced insulin secretion and IGF-1 levels both tend to be low in patients with CF, yet both play a central role in maintaining healthy muscle. Insulin treatment may increase hepatic IGF-1 production and attenuate cytokine-induced protein breakdown, having beneficial effects on maintenance of skeletal muscle mass and nutritional status in these patients.

Normal fasting glucose values (and insulin sensitivity) in many patients with CF may explain the unfortunately often delayed detection of insulinopenia and frequent lack of timely recommendation for insulin replacement. Depot insulin injections may not be the most appropriate first line treatment, rather, we strongly advocate - independently of fasting glucose and A1c values, close clinical observations in individuals with CF as important bases to propose food-related (preprandial injection) insulin therapy.

Conclusions

In summary, we conclude that despite markedly impaired insulin secretion, oral glucose suppressed FFA to a similar extent in patients with CF as in healthy subjects. Residual insulin in the face of increased energy expenditure (and possibly adiponectin-enhanced-FFA oxidation) and apparently normal insulin sensitivity appears to be sufficient for maintaining FFA homeostasis in patients with CF.

Conflicts of Interest Disclosure

Dr. Schnyder reports personal fees from Philhuman Stiftung during the conduct of the study. There are no conflicts of interest.

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