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Letter to the Editor

Insulin secretion abnormalities in patients with cystic fibrosis

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The oral glucose tolerance test (oGTT) is the test of choice for the diagnosis of cystic fibrosis-related diabetes (CFRD). Usually, CFRD justifies insulin therapy. Based on an assessment of the insulinogenic index (IGI_P, calculated as proposed by Phillips), Wooldridge et al. suggest that insulin secretion may be impaired in exocrine pancreatic sufficient CF (CF-PS) patients [1]. These patients have traditionally not been considered at risk [2]. Wooldridge et al. compared seven CF-PS patients (all with normal glucose tolerance) aged 12.6 ± 5.2 years with a reference group of healthy young adults aged 19.8 ± 1 years and documented lower IGI_P in the former. Bone maturation and puberty result in an increase in insulin resistance and insulin secretion in healthy individuals [3], and normal glucose tolerance is maintained as long as the pancreatic β-cells can adapt to increasing demands [3,4]. Along this line, it could be anticipated that the younger (including CF-PS) subjects with their presumably higher insulin sensitivity would have a lower IGI than the adult (healthy control) subjects. We therefore strongly believe that it would be important to compare the IGI of individuals of the same age, and thus, we checked their findings in groups of adult (≥ 18 year-old) CF patients and controls at our centre.

We routinely perform oGTT in our CF patients according to European CF Society management guidelines (unless they are known for previous fasting plasma glucose ≥ 7.0 mmol/l or diabetes treatment). We measure not only venous plasma glucose but also serum insulin at baseline (mean of two samples) and 30, 60, 90, and 120 min after glucose load. Subjects without dysglycaemic disorders served as controls [4]. Whole body insulin sensitivity index (ISI_M, as proposed by Matsuda and DeFronzo) and IGI_P were calculated as described [1,4]. Local ethics committee approval and written informed consent were obtained.

Ninety-six pancreatic insufficient (CF-PI) and 9 CF-PS patients were included and compared to 21 controls (Table 1). Overall, more than half of the CF-PI patients but none of the CF-PS were Phe508del homozygous. All 9 patients in the CF-PS group had CF-causing mutations; 7 were heterozygous for Phe508del and 2 had other genotypes. Within the group, there was a considerable heterogeneity, just given by the fact that in 3 of them the oGTT was performed as a part of lung transplantation assessment. In eight of the 9 CF-PS patients, we found CF-typical airway pathogens (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, Burkholderia cepacia complex and *Stenotrophomonas maltophilia*). Fecal elastase levels (normal reference >200 μg/g stool) were >400 μg/g in 7 cases; in 2 cases we had no documentation of fecal elastase. None of the CF-PS patients were on supplementation with pancreatic enzymes. The mean age was similar in all three groups. The CF-PI had lower body mass index (BMI), higher glycosylated haemoglobin (A1c) and fasting plasma glucose (FPG) than the CF-PS patients and the controls. First second expiratory volume (FEV_1) was on average lower in CF-PI than in CF-PS patients. Two hours after glucose intake, plasma glucose was higher in CF-PI than in CF-PS patients and controls. Based on a glucose value ≥ 11.1 mmol/l 2 h after oral glucose intake (2hPG), a new diagnosis of CFRD was made in 30 of 96 CF-PI (and in none of the 9 CF-PS) patients. ISI_M was similar in all groups, but IGI_P was markedly lower in CF-PI patients when compared with controls. Mean IGI_P tended to be lower in CF-PS patients compared with controls, but the 95% confidence interval overlapped (Table 1). Our results share an important limitation with the study we discuss here [1]: the number of CF-PS patients cared for at our adult CF centre and lung transplant program in Zurich is quite low.

We agree that CF patients should be considered a priori at risk for insulin secretion abnormalities and that the IGI

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Table 1
Demographic data (mean ± SD), BMI, cystic fibrosis transmembrane conductance regulator (CFTR) genotype, FEV_1, and oGTT data of CF-PI, of CF-PS, and of subjects without CF (controls).

	CF-PI (30 with CFRD/66 without CFRD)	CF-PS	Controls
Number (n)	96	9	21
Male/female (n)	54 (14/40)/42 (16/26)	4/5	11/10
Age (y)	27 ± 8	27 ± 7	29 ± 6
CFTR genotype [a]	58/27/10/1	0/7 [b]/2 [c]/0	0/0/0/21
BMI (kg/m^2)	19.4 ± 2.9 †	23.6 ± 5.7	23.3 ± 4.5
FEV_1 (%)	44 ± 26	56 ± 30	Not analyzed
A1c (%)	5.9 ± 0.6 ***	5.4 ± 0.4	5.4 ± 0.2
FPG (mmol/l)	5.1 ± 0.8 **	4.7 ± 0.3	4.7 ± 0.5
2hPG (mmol/l)	9.3 ± 4.2 ***	6.2 ± 2.0	5.8 ± 1.2
AUC glu (mM min)	1162 ± 286 †	996 ± 111 ***	833 ± 110
$Ins_{0'}$ (pmol/l)	109 ± 40	102 ± 38	110 ± 46
AUC ins (pM·min)	46,471 ± 21,458 **	63,752 ± 15,065	59,995 ± 34,415
ISI_M (1/mMpM)	8.8 ± 3.5	8.1 ± 2.2	9.6 ± 3.3
IGI_P ($\Delta Ins_{0-30'}$/ $\Delta PG_{0-30'}$; pM/mM)	47 ± 37 † 22 (17–27)/59 (50–68)	94 ± 54 * 94 (52–135)	185 ± 131 185 (125–244)

Venous plasma glucose was measured by the hexokinase method and serum insulin by solid phase radioimmunoassay; CIS Bio International, Oris Industries, Gif-Sur-Yvette, France. Areas under curve of glucose and insulin (AUC glu and AUC ins), insulin sensitivity index (ISI_M) and insulinogenic index (IGI_P) were calculated as described elsewhere [1,4]. In case of IGI_P, data are also shown as means and 95% confidence interval, including 2 separate subgroups within the 96 CF-PI patients, the 30 patients with and the 66 without CFRD. The p values represent the comparison CF-PI or CF-PS vs controls.

[a] Phe508del homozygous/heterozygous/other genotype/not analyzed.
[b] Mutation no. 2: R347P/R347P/R347P/A455E/4382delA/4382delA/S945L.
[c] Mutation nos. 1 and 2: R347H, 405 + 1GA/P5L, CFTRdele14b–17b.
* $p = 0.55$.
** $p = 0.05$.
*** $p = 0.001$.
† $p = 0.0001$.

(assessing insulin secretion 30 min after glucose ingestion) is useful to detect the delayed insulin secretion as it is characteristic for most of the adult CF patients; the decrease in IGI usually precedes the development of impaired glucose tolerance and CFRD. A decrease in IGI may be comparably sensitive to a history of exocrine pancreatic insufficiency and low fecal elastase in the detection of pancreatic failure, but the question remains whether intrinsic insulin secretion defects occur in truly CF-PS patients. It is important to note that IGI values quoted in our patient cohort are not directly comparable to those reported by Wooldridge et al. as insulin measurements have not yet been standardized limiting their general clinical utility. Thus, appropriate reference ranges and control groups are required.

At the present time, we have to conclude that – using properly age-matched controls – we cannot unequivocally confirm the hypothesis of Wooldridge and colleagues [1]. An intrinsic insulin secretion defect in β-cells of CF patients (irrespective of exocrine pancreatic inflammation-induced damage) can be neither excluded nor supported.

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