Insulin release in cystic fibrosis

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Kjellman, N-I. M., and Larsson, Y. (1975). *Archives of Disease in Childhood*, **50**, 205. **Insulin release in cystic fibrosis.** Early insulin response to rapid intravenous injection of glucose was studied in 7 cases of cystic fibrosis aged 8 months to 9½ years. Plasma insulin was measured with a radioimmunological method. Blood glucose values were determined and the glucose disappearance rate (k_G) calculated. In all children except the youngest one the early insulin response values were low compared with normal children. The k_G -values were normal and correlated neither to the duration of clinical symptoms, nor to the patients' actual clinical condition measured by means of the Shwachman score. The explanation of the decreased insulin response is probably the progressive fibrosis of the pancreas. This may also explain the reported increased incidence of diabetes mellitus in cystic fibrosis. Comparison is made with the condition in pancreatic fibrosis in rabbits, produced through duct ligation.

In the extensive published reports on cystic fibrosis (CF) interest has been focused mainly on the exocrine function of the pancreas and on respiratory manifestations of the disease. Relatively little attention has been given to the function of the pancreatic islets. However, as the survival of patients with CF has improved and long-term follow-up studies have become possible, it has been maintained that the occurrence of diabetes mellitus in these patients is more than a chance occurrence. Thus, the incidence of diabetes was 10/1300 in the series reported by Rosan, Shwachman, and Kulczycki (1962) and 2/126 in the long-term study by Shwachman, Redmond, and Khaw, published in 1970. As the average incidence of onset of diabetes before the age of 15 years is 1–2/1000 (Sterky, 1963; Beardmore and Reid, 1966), the reported figures for the incidence of diabetes among patients with CF are higher than if the two diseases had occurred independently.

Furthermore, some authors have found decreased carbohydrate tolerance and diminished insulin response to glucose administration in patients with CF (Milner, 1969; Handwerger *et al.*, 1969; Milunsky *et al.*, 1971). However, in these studies the early response of insulin release to glucose (ER) has not been analysed, although ER probably is the best indicator of the capacity of the β -cell to produce insulin (Cerasi and Luft, 1967a, b; Nosslin, Sterky,

and Thorell, 1972). For this reason we found it of interest to study glucose tolerance and ER in children with CF.

Material

Seven children with CF were investigated, 2 girls and 5 boys whose ages ranged from 0·7 to 9·5 years (Table I). There were two pairs of sibs (Cases 1–3 and 4–6), but otherwise there was no family history for CF. The clinical picture was typical in all cases, including fatty stools, chronic respiratory manifestations, and a positive sweat test. All cases were given pancreatic substitution therapy, multivitamin preparations and a high protein diet. Antibiotics and other symptomatic therapy for respiratory problems were given on an individual basis. A Shwachman score (Shwachman and Kulczycki, 1958) was determined in all cases giving a mean value of 85, range 60–100.

Methods

Two patients were studied in hospital, the remaining 5 were outpatients. Intravenous glucose tolerance tests were performed with an indwelling catheter and a rapid solution of glucose in a dosage of 0·5 g glucose/kg body weight. Venous blood was drawn for determination of glucose and insulin before the injection and at 5, 7, 12, 30, 45, and 60 minutes thereafter. Blood glucose was determined with a colorimetric hexokinase assay system according to Carroll, Smith and Babson, (1971). Plasma insulin was determined by radioimmunoassay using a commercial test kit (Pharmacia Phadebas). Glucose tolerance was calculated as the disappearance rate of glucose (k_G) according to Ikko and Luft (1957). ER

TABLE I
Patients

Case no.	Sex	Age (years)	Age at diagnosis (years)	Height/age (SD)	Weight/height (SD)	Shwachman score
1	M	9.5	1.2	-1.0	-0.6	85
2	M	6.8	3.1	-1.0	± 0	90
3	M	6.7	0.3	± 0	± 0	100
4	F	5.2	0.7	-1.3	-1.5	75
5	M	5.0	4.3	-2.1	-2.2	60
6	M	1.8	0.1	-3.2	-0.6	90
7	F	0.7	0.3	-1.9	-1.2	95
Mean		5.1	1.4	-1.5	-0.9	85

was calculated according to Nosslin *et al.* (1972) and expressed as $\mu\text{U}/\text{ml}$ plasma. With this method ER indicates the amount of insulin that has been produced during the first 10 minutes of the test, and the formula used implies a correction for the amount of insulin that disappears from the circulation during the same period.

Results

The results of the intravenous glucose tolerance tests are shown in Fig. 1 and Table II, and individual k_G and ER values in Table III. The mean value for k_G was 1.95, which is within the range of healthy nondiabetic children (von Euler and Larsson, 1962). The mean value for ER was 22.0. A typical case (Case 1) is shown in Fig. 2. This was the oldest patient in the study who in spite of a marked rise in blood glucose and a k_G value of 1.98 had an insignificant insulin release and an ER value of 16.1. Cases 2-6 gave similar curves, while Case 7, (Fig. 3) the youngest patient in the series, had considerably higher insulin levels and an ER

FIG. 1.—Glucose tolerance tests. Mean values ± 1 SD for blood glucose and insulin.

value within normal limits. The effect of intravenous glucose administration on plasma insulin in healthy children has been studied by Weber (1971) (Fig. 4). For the sake of comparison, the values of

TABLE II
Results of intravenous glucose tolerance tests

Case no.	Time (min)							
	0	5	7	12	15	30	45	60
A. Blood glucose (mg/100 ml)								
1	72	246	280	226	—	164	126	81
2	90	258	272	228	246	164	120	80
3	76	190	232	220	—	134	80	58
4	50	222	200	182	160	160	134	100
5	114	—	478	—	480	270	210	160
6	66	200	200	182	—	120	84	62
7	111	—	—	170	149	123	104	103
B. Plasma insulin ($\mu\text{U}/\text{ml}$)								
1	3.4	10	12	12	—	10	9	7
2	10	26	25	12	13	21	18	23
3	<3.2	8	12	8	—	7	<3.2	<3.2
4	9	27	29	25	—	19	20	16
5	4	10	11	9	—	9	10	6
6	5	16	14	10	—	9	9	18
7	4	58	39	22	—	<3	<3	<3

TABLE III
Glucose tolerance tests

Case no.	k_G	ER
1	1.98	16.1
2	2.23	13.4
3	2.57	11.2
4	1.28	33.3
5	1.78	9.8
6	2.20	13.3
7	1.61	57.4
Mean	1.95	22.0

 k_G Glucose disappearance rate; ER early insulin response.

FIG. 2.—Case 1. Glucose tolerance test.

FIG. 3.—Case 7. Glucose tolerance test.

Weber have been used to calculate ER with the same method as used in this study. The result is shown in Table IV, which also includes the mean ER value of healthy adult men, 22–28 years of age, from a study by J. Thorell, (personal communication, 1973). The ER values of the CF children were significantly lower than those of both healthy children and healthy adults (Fig. 5).

FIG. 4.—Intravenous glucose tolerance test in healthy children 2–14 years of age (adapted from Weber, 1971).

TABLE IV
 k_G and ER: mean values from 3 different studies

	k_G	ER
Normal adult men (29) Aged 22–28 years (J. Thorell, personal communication, 1973)	> 1.1	57.4
Normal children (10) Aged 2–14 years (Weber, 1971)	2.31	93.4
Children with CF (7) Aged 0.7–9.5 years (this study)	1.95	22.0

FIG. 5.—Early insulin response in children with CF compared with that in normal adults (J. Thorell, personal communication, 1973).

Discussion

Our results show that although none of the 7 CF children had overt diabetes mellitus nor

decreased glucose tolerance as measured in the intravenous test and was evident from their normal k_G -values, all but one showed a decreased early insulin release in response to intravenous glucose. These findings may be compared with those of other investigators. Thus Milner (1969) found that the majority of 61 children with CF had a lower insulin response to oral glucose than healthy children, though only 18 of these patients had decreased glucose tolerance. In the cases of Handwerger *et al.* (1969), 13 of 31 CF patients had decreased oral glucose tolerance combined with delayed insulin response. In 9 of these cases intravenous tolerance tests again showed delayed insulin release. Milunsky *et al.* (1971) studied 15 CF patients with oral glucose tests and found the same type of insulinopenia without concomitant glucose intolerance. However, as both the diagnostic criteria and the methods used in these earlier reports differ considerably, a direct comparison between the results is not possible. The overall conclusion must be, however, that our study has confirmed that the capacity for insulin release is decreased in CF. CF may be considered as a pre-diabetic condition, as Cerasi and Luft (1967a, b), Nosslin *et al.* (1972), and others have shown that a poor early insulin response is a characteristic of the prediabetic state. Our findings are also in agreement with the clinical experience that overt or chemical diabetes is more common among CF patients than in the average population, particularly in cases of CF with a long observation time (Kaiser, Zuppinger, and Joss, 1970; Rosan *et al.*, 1962; Shwachman *et al.*, 1970).

There are several possible explanations for the diminished insulin production in CF. One possibility might be that the gene for CF is linked to that for diabetes, but the absence of an increased incidence of CF among diabetics or in their families is against this hypothesis. Another explanation could be that the generalized dysfunction of secretory cells, characteristic of CF, also occurs in the β -cells of the pancreas. However, as diabetes usually appears late in the course of CF (Gracey, 1971), it seems more likely that it is a secondary rather than a primary manifestation of CF. Milner, in whose study the insulin response was poorer in oral than in intravenous glucose tolerance tests, has suggested that defects in the secretion of glucagon-related hormones from specific intestinal mucosal cells might be of aetiological importance. This hypothesis does not seem to explain the poor insulin response to intravenous glucose, however. A low glucose tolerance could also be secondary to malnutrition, which is found in some CF patients.

Insulinopenia occurs, however, in CF patients with a good nutritional state and high Shwachman score figures. This was the case in our study.

Handwerger *et al.* (1969) have suggested that the advanced structural alterations which are present in the exocrine parenchyma of the pancreas in CF also affects the islet function. The histological picture is characterized by a progressive fibrosis which usually involves the islet tissue as well and which might lead to an architectural disorganization of such an order of magnitude as to involve the blood supply and function of the islets. A decreased islet volume is a common feature in CF in analogy with the conditions in experimental pancreatic fibrosis secondary to ligation of the main pancreatic duct (Larsson, 1958; see Fig. 6). A compensatory mechanism to this shrinkage is represented by the new formation of islet cells,

FIG. 6.—Size of pancreatic islet tissue in duct-ligated, alloxan-diabetic, and normal rabbits (Larsson, 1958). A, untreated rabbits; B, rabbits with ligated pancreatic duct; C, alloxan-diabetic rabbits.

nesidioblastosis, which occurs both in healthy young children (Meissner, 1954), experimental animals, and in patients with CF (Brown and Madge, 1971). This might give temporary protection against or postpone the onset of diabetes. An analogy is the resistance towards the diabetogenic action of alloxan which is found in duct-ligated animals (Edström, 1972; Larsson, 1956; Walpole and Innes, 1946). Nesidioblastosis seems to be more active in young subjects. In CF decreasing glucose tolerance and increasing incidence of overt diabetes with age might be explained by the fact that the relative protection against complete fibrotic islet destruction which nesidioblastosis provides during the early period of life, is gradually lost when the patient grows older and loses the capacity to form new islet cells.

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