Glucose tolerance in cystic fibrosis

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Abstract

Glucose tolerance was evaluated in 356 living and dead patients with cystic fibrosis who were recorded at the Danish Cystic Fibrosis Centre. Twenty two patients (6%) were treated elsewhere, 25 (7%) were unable, unwilling or too young (age <2 years) to participate; 309 patients (87%) were therefore eligible for the study of whom 99 (32%) were dead and 210 (68%) were alive. Of the dead patients, 13 also had diabetes mellitus (13%). Of the living patients (median age 14 years, range 2-40), nine (4%) were known to have diabetes and all were being treated with insulin. In the remaining 201 patients an oral glucose tolerance test (1.75 g/kg body weight, maximum 75 g) was carried out. A total of 155 patients (74%) had normal glucose tolerance, 31 (15%) had impaired glucose tolerance, and 15 (7%) had diabetes mellitus according to the WHO criteria. The percentage of glycated haemoglobin (HbA_{1c}) (reference range 4.1-6.4%) increased significantly as glucose tolerance decreased: when glucose tolerance was normal the median was 5.2%; when it was impaired the figure was 5.5%; in patients whose diabetes was diagnosed by the oral glucose tolerance test it was 5.9%; and in patients already known to have diabetes mellitus it was 8.6%. The incidence and prevalence of impaired glucose tolerance and diabetes mellitus increased with age. From the age of 15 to 30 years the decrease in the prevalence of normal glucose tolerance was almost linear. Within this age span the proportion of patients with cystic fibrosis with normal glucose tolerance was reduced by roughly 5%/year. Only 35% (95% confidence interval (CI) 22 to 48%) of the patients with cystic fibrosis who were alive at the age of 25 years had normal glucose tolerance; 32% (95% CI 14 to 49%) were diabetic.

The prevalence of glucose intolerance in cystic fibrosis is rapidly increasing with age; its potentially harmful effect on the prognosis of cystic fibrosis is of increasing importance as the length of survival of these patients increases.

Cystic fibrosis is an autosomal recessive disorder that affects many organs including the pancreas. In addition to insufficiency of pancreatic exocrine function, there is a high incidence of pancreatic endocrine dysfunction. Early studies described glucose tolerance in the disease,^{1 2} but an association between diabetes mellitus and cystic fibrosis was recognised in

1955.³ Since then many investigators have reported glucose intolerance and diabetes mellitus as common problems in cystic fibrosis.⁴⁻²³

The prevalence of glucose intolerance in cystic fibrosis increases with age,⁵ and because of the increased life expectancy of patients with cystic fibrosis,^{24 25} the possible adverse effect of glucose intolerance on prognosis has become increasingly relevant in recent years.²⁶ Previous studies have included only a limited number of patients, often highly selected, and have applied various diagnostic criteria of glucose intolerance. We therefore studied the prevalence of impaired glucose tolerance and diabetes mellitus (WHO criteria) in a large group of unselected patients followed up at the Danish Cystic Fibrosis Centre.

Subjects and methods

Since the foundation of the Danish Cystic Fibrosis Centre in 1949, 356 patients (181 men) have been followed up at the centre. The diagnosis of cystic fibrosis was based on the presence of abnormal electrolyte concentrations in sweat and a typical clinical picture.^{27 28} By October 1989, 99 patients (50 men) had died, and 22 (12 men) had been treated elsewhere. From the records of the dead patients, information was obtained about sex, age at death, family history of diabetes, presence or absence of diabetes mellitus (diagnosed by raised blood glucose concentration or glycosuria, or both), and, if they were diabetic, the age at the time of diagnosis of the diabetes.

Of the 235 patients (119 men) currently attending the clinic regularly, 210 (89%) patients (104 men) were willing to participate in the study. Reasons given for not taking part were: unwillingness (n=9), inability because of mental disease (n=3), and age less than 2 years (n=13), which was the minimal age for inclusion. The median age of the 210 patients was 14 years (range 2-40), median height 152 cm (range 81-190), and median weight 40 kg (range 10-84). One hundred and twenty three patients had chronic infections with *Pseudomonas aeruginosa*.

We recommend a normal balanced diet for our patients preferably one with a high energy content. We did not give nutrients or fluids either parenterally or by nasogastric tube.

Nine of the 210 patients were known to have diabetes mellitus (4%); all were being treated with insulin. The remaining 201 patients (99 men) underwent an oral glucose tolerance test according to the WHO recommendations.²⁹ Briefly, after an overnight fast the patient was

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given 1.75 g glucose monohydrate/kg body weight (maximum 75 g), dissolved in 2–300 ml of lemon flavoured water, over 3–4 minutes. Capillary plasma glucose concentrations were measured before, and 60 and 120 minutes after, the glucose load. During the study the patient was resting, fasting, and did not smoke.

After completion of the glucose tolerance test, blood was sampled for estimation of glycated haemoglobin (HbA_{1c}), assessment of measures of liver function, and presence of *P aeruginosa* precipitins. A pulmonary function test was done for all patients over 6 years old. Finally, the patient (or the relatives) was asked about the daily number of pancreatic enzyme capsules taken (used as a measure of the exocrine pancreatic function), the family history of diabetes, and the use of any drugs with a potential for influencing glucose tolerance.

The capillary plasma glucose concentration was measured with a glucose dehydrogenase method (Merck).³⁰ According to the WHO criteria,²⁹ a capillary plasma glucose concentration of 8.8 mmol/l or less at two hours was considered as normal glucose tolerance, a value of 8.9–12.1 mmol/l indicated impaired glucose tolerance, and a value of 12.2 mmol/l or more was diagnostic of diabetes mellitus.

HbA_{1c} was measured as previously described³¹; the reference range is 4.1–6.4%. Precipitins against *P aeruginosa* were measured by Høiby's method.³²

Pulmonary function was assessed by forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁), and recorded on an electronic spirometer (Spiroton, Draeger). The results are expressed as percentages of the reference values for sex and height in patients less than 20 years old³³ and sex, height, and age in patients aged 20 years or more.³⁴

The study was conducted in accordance with the Declaration of Helsinki (Tokyo revision) and was approved by the municipal medical ethics committee of Copenhagen and Frederiksberg. Informed consent was obtained from all participants or their parents, or both.

The statistical evaluation includes non-parametric tests (Kruskal-Wallis test, Mann-

Whitney test, Fisher's exact test) and life table analysis; a probability of less than 0.05 (two-tailed) was accepted as significant, and 95% confidence intervals (CI) were calculated. Data are presented as median (ranges) unless otherwise stated.

Results

Thirteen of the 99 dead patients had had diabetes mellitus (13%); five had been treated with insulin. In 74 patients (75%) diabetes mellitus had not been diagnosed, and in 12 patients (12%) it was not possible to establish whether they had been diabetic or not. Diabetes mellitus was diagnosed at the median age of 16 years (range 6–32). Four patients had been diabetic for a median of 4 years (range 3–13) before death (two were treated with insulin), whereas nine became diabetic within their last year, including four in whom glycosuria was a terminal event. The median age of the diabetic patients was 23 years (range 6–33) at the time of death. There was a family history of diabetes mellitus in eight cases, two of whom were diabetic themselves.

Glucose intolerance was found in 55 of the 210 who were still alive (26%), including 24 with diabetes mellitus (11%). The latter prevalence does not differ from the prevalence of 13% among the dead patients (p=0.80).

HbA_{1c} increased significantly as glucose tolerance decreased (table). In patients with normal or impaired glucose tolerance and with diabetes mellitus diagnosed by glucose tolerance test, the percentages of HbA_{1c} were, however, within or close to the reference range, and the ranges of HbA_{1c} values overlapped between groups though to a lesser extent for known diabetes mellitus.

In the patients known to have diabetes, it had been diagnosed at a median age of 15 years (range 3–24). This is no different from the median age at diagnosis (16 years) in the 13 deceased patients with diabetes (p=0.46). Only two patients developed diabetes before the age of 10 years (at the ages of 3 and 8 years, respectively). They both presented with ketonuria and

Characteristics of endocrine and exocrine pancreatic function and pulmonary function in 210 patients with cystic fibrosis classified according to WHO criteria of glucose tolerance. Data for FEV₁ and FVC measurements are taken from 115 patients with normal glucose tolerance and 28 with impaired glucose tolerance, all more than 6 years old. Figures are median (range) except where otherwise stated

	Normal glucose tolerance	Impaired glucose tolerance	Diabetes mellitus		
			Diagnosed by oral glucose tolerance test	Known cases	Total
No (%) of patients	155 (74)	31 (15)	15 (7)	9 (4)	24 (11)
Age (years)	11.4 (2–38)	18.3 (4–28)*	22.0 (14–40)*§	20.0 (14–28)*	21.5 (14–40)*§
Plasma glucose concentration (mmol/l):					
Fasting	5.3 (3.8–6.8)	5.3 (3.9–6.9)	5.7 (4.2–8.0)†	Not known	Not known
After one hour	10.0 (5.3–16.0)	11.5 (8.7–17.4)*	15.4 (10.5–21.0)*‡	Not known	Not known
After two hours	6.4 (2.5–8.8)	10.3 (8.9–12.0)	14.6 (12.4–21.0)	Not known	Not known
HbA _{1c} (%)	5.2 (4.1–6.2)	5.5 (4.4–6.3)*	5.9 (5.2–7.0)*§	8.6 (5.7–11.8)*‡	6.4 (5.2–11.8)*‡
FEV ₁ (% of normal)	77 (16–128)	61 (27–121)†	59 (25–100)	39 (26–92)*	52 (25–110)*
FVC (% of normal)	89 (34–150)	84 (44–123)	75 (45–126)	57 (28–101)*§	72 (28–126)†
No of precipitins against <i>P aeruginosa</i>	1.2 (0–46)	21 (0–45)*	30 (0–44)*	28 (0–44)†	30 (0–44)*
No of capsules/day pancreatic enzymes	30 (0–195)	30 (0–135)	21 (0–44)*§	36 (12–110)	24 (0–110)

Compared with normal glucose tolerance: *p<0.01; †p<0.05.
Compared with impaired glucose tolerance: ‡p<0.01; §p<0.05.
Compared with diabetes diagnosed by oral glucose tolerance test: ||p<0.01; ¶p<0.05.

Figure 1 Annual percentage of patients with cystic fibrosis whose glucose tolerance deteriorated from normal to impaired glucose tolerance or diabetes mellitus (hatched columns), and from normal or impaired glucose tolerance to diabetes mellitus (solid columns) plotted against age.

Figure 2 Percentage of patients with cystic fibrosis and normal glucose tolerance plotted against age in a life table. The dots indicate 95% CI.

have needed insulin ever since, making the coincidence of cystic fibrosis and insulin dependent (type 1) diabetes mellitus likely.

A total of eight patients were receiving corticosteroids at the time of the study. In three diabetic patients (two with known diabetes and one who had been diagnosed after a glucose tolerance test), the onset of diabetes was preceded by prednisone treatment for allergic bronchopulmonary aspergillosis for 22 months, four months, and less than one month, respectively; a fourth patient, diagnosed by glucose tolerance test and diabetic for one year, had to start insulin injections after prednisone treatment of aspergillosis lasting two months. Another four patients treated with prednisone for aspergillosis did not develop diabetes. No patient received thiazides.

The median age of the patients in the different classes of glucose tolerance increased as glucose tolerance decreased (table), but the age of the patients in the two classes of diabetes mellitus (those diagnosed by glucose tolerance test and those already known) did not differ significantly. Two of the 117 patients who were less than 15 years of age (2%) were diabetic compared with 22 of 93 patients aged 15 years or more (24%; $p < 0.01$).

By life table analysis we estimated the incidence and prevalence of different classes of glucose intolerance. The annual incidences of patients deteriorating from normal to impaired glucose tolerance or diabetes mellitus, and from normal or impaired glucose tolerance to diabetes mellitus, calculated for five year age groups, both steadily increased over the age of 10 years (fig 1). In the age group 10–15 years the rate of deterioration from impaired glucose tolerance to diabetes mellitus is about 2%/year, increasing to about 17%/year in the age group 25–30 years; in parallel, the incidence of diabetes mellitus increases from about 1 to 13%/year in the same age groups.

The prevalence of normal glucose tolerance decreases with age (fig 2); from the age of 15 to 30 years the decrease is almost linear. Within this age group the proportion of patients with normal glucose tolerance is reduced by roughly 5%/year. Thus, 86% (95% CI 80 to 93%) of the patients have normal glucose tolerance at the age of 15 years, whereas only 35% (95% CI 22 to 48%) have normal glucose tolerance at the age of 25; at the latter age 32% (95% CI 14 to 49%) are diabetic.

Twenty one patients gave a family history of diabetes (including two pairs of siblings). Four (19%) of these patients had diabetes (two were being treated with insulin) compared with 20 (11%) of the 189 patients who did not give a family history of diabetes ($p = 0.25$).

Median FEV₁ was lower in patients with impaired glucose tolerance or known diabetes mellitus, and in all diabetic patients compared with those with normal glucose tolerance, whereas the differences between the normal group and those diagnosed by glucose tolerance test, and the impaired group and the known diabetic group were not significant (both $p < 0.10$) (table). FVC was lower in patients known to have diabetes than in all other groups, and lower in diabetic patients than in patients with normal glucose tolerance (table). Precipitins against *P aeruginosa* were lower in patients with normal glucose tolerance than in all other groups (table). The daily intake of pancreas enzyme capsules was lower in patients with diabetes diagnosed by glucose tolerance test than in all other groups (table).

Discussion

This first large cross sectional study of oral glucose tolerance in unselected patients with cystic fibrosis over the age of 2 years confirms that the prevalence of glucose intolerance (26%) in cystic fibrosis is high. For comparison, in 12 studies comprising a total of 284 patients an oral glucose tolerance test identified 21–75% of the patients as being glucose intolerant (the mean was 41%, but varying criteria for glucose tolerance and diabetes mellitus were used).^{4 5 7 9 10 13–16 18 20 21}

Eleven per cent of our patients were diabetic; the retrospective part of our study showed an almost similar prevalence of diabetes mellitus in the dead patients. Seventeen studies, in which various criteria for selection and diagnosis were applied, included a total of 1510 patients

of various ages.^{2 4-8 11 12 14 16-23} Of these patients, 134 (8.9%, range 0–17%) were diabetic. The mean prevalence of diabetes mellitus calculated from these studies was apparently the same (7–9%), whether an oral glucose tolerance test (n=266),^{2 4 5 7 14 16 18 20 21} random blood glucose values (n=448²²), the presence of glycosuria (n=221^{6 8 11 12}), or non-stated diagnostic procedures (n=575^{17 19 23}) were used for diagnosis.

Impaired glucose tolerance, which in some populations is said to accompany a greater risk of developing arterial disease than normal glucose tolerance,²⁹ was found in 15% of our patients. In seven other studies, again with varying criteria for the diagnosis of impaired glucose tolerance, the mean prevalence was 30% (n=201, range 18–56%).^{5 7 13 15 17 19 20}

The prevalence of diabetes mellitus reported here is therefore higher, though those of impaired glucose tolerance and both types of glucose intolerance considered together are lower than found previously. No obvious explanations exist for this discrepancy. The influence of differences between the patient groups in age or other selection criteria or from varying diagnostic criteria for the different classes of glucose tolerance may be of importance. It is, however, beyond any doubt that the incidence and prevalence of glucose intolerance—impaired glucose tolerance as well as diabetes mellitus—is much higher in patients with cystic fibrosis than in any other age matched group.

It is not known whether glucose intolerance influences the prognosis of cystic fibrosis. Progressive clinical deterioration in patients with cystic fibrosis and diabetes mellitus has been reported by some investigators,^{5 22} but was not detected by others.^{7 13 18 20} We observed that FEV₁ decreased as glucose tolerance decreased, as did FVC, and there were more precipitins against *P. aeruginosa* found in patients with all classes of glucose intolerance compared with normals. It is doubtful, however, whether these findings reflect a causal relationship between glucose intolerance and cystic fibrosis in general, but merely the difference in age (equal to the duration of cystic fibrosis) between the different groups of glucose tolerance. The daily intake of pancreatic enzyme—a rough estimate of exocrine pancreatic function—was for unknown reasons lower in patients with diabetes diagnosed by glucose tolerance test than in all other patients. Using more up to date techniques, a parallel loss of exocrine and endocrine pancreatic function has been shown.¹⁴

Although diabetes mellitus in cystic fibrosis is generally considered mild in itself,^{5 10 12} no data exist to substantiate the statement. The development of the late diabetic complications, however, as are seen in other states of diabetes mellitus like insulin dependent diabetes mellitus and non-insulin dependent (type 2) diabetes mellitus, has only been described in a few patients with both cystic fibrosis and diabetes mellitus.^{18 35-37}

Until reliable studies confirm the 'mild' nature of the glucose intolerance in cystic fibrosis, both in itself and in its effect on the prognosis, we feel that diabetes mellitus in cystic fib-

rosis should be treated as carefully as diabetes mellitus of all types is treated in younger subjects. The question then arises of how to identify the patients with cystic fibrosis and glucose intolerance.

Clinical diagnosis prompted by symptoms of hyperglycaemia seems unreliable, as many diabetic patients are asymptomatic, including our own group of patients who were diagnosed by oral glucose tolerance test. The reliability of regular urine testing for glucose has not been systematically evaluated in patients with cystic fibrosis. According to the WHO recommendations,²⁹ the fasting blood glucose concentration alone should be considered less reliable as true fasting cannot be assured, which may lead to the false diagnosis of diabetes mellitus. If it is used, some diabetic patients will remain undiagnosed; in our study 87% of the 15 patients with diabetes mellitus diagnosed by oral glucose tolerance testing had fasting capillary plasma glucose values below the diagnostic value of 7.8 mmol/l.²⁹ Finally, measurement of HbA_{1c} has been suggested as a screening procedure.^{13 20} In our study, however, 73% of the patients diagnosed by oral glucose tolerance test had HbA_{1c} values within the reference range. In contrast to Stutchfield *et al.*, we found a HbA_{1c} value above the reference range diagnostic of diabetes mellitus.²⁰ Serial determination of HbA_{1c} values has been suggested for the detection of impairment of glucose tolerance,^{13 20} but its value remains to be established.²²

We have demonstrated that oral glucose tolerance tests are reliable in the detection of diabetes mellitus in patients with cystic fibrosis. We intend to review our patients over the age of 2 years annually to determine the ages and intervals at which it would be reasonable to recommend oral glucose tolerance tests as part of clinical practice. At present, we hypothesise that only patients over the age of 10 years will need regular tests, as our two patients who developed diabetes mellitus below this age limit both had frank symptoms of diabetes at onset.

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Insect stings

Children who are stung by insects do better on the whole than adults in that they are less likely to have severe or life threatening reactions. Recent work from the Johns Hopkins Medical School has provided information about the use of desensitising injections (Valentine MD *et al*, *New England Journal of Medicine* 1990;323:1601-3). A total of 242 children aged from 2 to 16 years had had a generalised reaction confined to the skin after an insect bite or sting and had positive skin tests with one or more of five insect venoms. Sixty eight of the children were given a series of desensitising injections using the appropriate venom. On follow up about half of all the children were stung again. In the treated group 1.2% of subsequent stings gave rise to systemic reactions but 9.2% did so in the untreated children. None of the reactions was serious.

The authors conclude that immunotherapy is effective in preventing systemic reactions after subsequent stings but that, as such reactions are almost always fairly mild, the treatment is not usually necessary. The study does not show whether immunotherapy would prevent severe reactions but such a study will probably never be done as it is calculated that it would need 17 000 patient years in both treated and untreated groups. An editorial in the same issue recommends treating all adults with a systemic reaction and children who have had a severe reaction (laryngeal oedema, asthma, or anaphylactic shock).¹ If treatment is offered it should be with venom and not with whole body extracts which are deemed 'practically inert'.²

ARCHIVIST

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