Glucose tolerance in patients with cystic fibrosis: five year prospective study

Susanne Lanng, Annelise Hansen, Birger Thorsteinsson, Jørn Nerup, Christian Koch

Abstract

***Objectives*—To study prevalence and incidence of diabetes mellitus in patients with cystic fibrosis.**

***Design*—Five year prospective study with annual oral glucose tolerance tests.**

***Setting*—CF Center Copenhagen, Denmark.**

***Subjects*—191 patients with cystic fibrosis aged above 2 years.**

***Main outcome measures*—Glucose tolerance, plasma glucose concentrations after fasting and after glucose loading, and haemoglobin A_{1c} levels.**

***Results*—Prevalence of diabetes increased from 11% (n=21) to 24% (n=46) during study, with annual age dependent incidence of 4-9%. Diabetes was diagnosed at median age of 21 (range 3-40). At diagnosis of diabetes, symptoms of hyperglycaemia were present in 33% of patients, fasting hyperglycaemia ($\geq$7·8 mmol/l) was seen in 16%, and increased haemoglobin A_{1c} levels (>6·4%) were seen in 16%. Impaired glucose tolerance implied higher risk for development of diabetes than normal glucose tolerance (odds ratio 5·6). In 58% of cases with impaired glucose tolerance, however, glucose tolerance was normal at next annual test. Normal glucose tolerance was found in only 37% of patients at all five tests. Within this group of patients, median plasma glucose concentrations after fasting and after glucose loading and haemoglobin A_{1c} levels increased by 6-8% during study.**

***Conclusions*—Prevalence and incidence of diabetes in cystic fibrosis patients was high and increased with age. Since hyperglycaemic symptoms, fasting hyperglycaemia, and increased levels of glycated haemoglobin did not reliably identify diabetes mellitus, we recommend annual oral glucose tolerance tests in all cystic fibrosis patients aged over 10 years.**

Introduction

In the past three decades survival of patients with cystic fibrosis has steadily improved to a median of about 30 years in several centres.[1-5] Following the increased life expectancy, glucose intolerance has been observed with increasing frequency in these patients.[6-8] We conducted a five year prospective study of glucose tolerance in a large unselected group of patients with cystic fibrosis in order to define the incidence of diabetes mellitus in cystic fibrosis.

Measurement of glycated haemoglobin has been suggested as an alternative to the oral glucose tolerance test for assessing glucose metabolism, and serial testing of parameters of glycaemic control has been suggested for diagnosing diabetes and predicting progression to diabetes in high risk groups (such as subjects with impaired glucose tolerance,[9] Pima Indians,[10] pregnant women,[11] patients with chronic pancreatitis,[12] and patients with cystic fibrosis[13 14]). We therefore annually measured glycated haemoglobin concentrations as well as performing oral glucose tolerance tests to test whether screening with this parameter could identify cystic fibrosis patients with undiagnosed diabetes. We also studied whether impaired glucose tolerance was a risk marker for the development of diabetes in such patients. Finally, we studied whether those patients who had normal glucose tolerance at all five oral glucose tolerance tests had stable plasma glucose concentrations after fasting and glucose loading and stable glycated haemoglobin levels.

CF Center Copenhagen, Department of Paediatrics, Rigshospitalet, Copenhagen, Denmark
Susanne Lanng, *research fellow*
Annelise Hansen, *nurse*
Christian Koch, *consultant*

Department of Medicine F, Hillerød Hospital, Hillerød, Denmark
Birger Thorsteinsson, *consultant*

Steno Diabetes Center, Gentofte, Denmark
Jørn Nerup, *professor*

Correspondence to:
Dr Lanng.

BMJ 1995;311:655-9

Subjects and methods

During 1989, 245 patients attended our cystic fibrosis centre. The diagnosis of cystic fibrosis was based on the presence of abnormal electrolyte concentrations in sweat and a typical clinical picture.[15 16] We included all 226 patients aged over 2 years in our five year prospective study (1989-93) with at least one annual oral glucose tolerance test. The study was conducted in accordance with the Declaration of Helsinki and was approved by the municipal medical ethics committee of Copenhagen and Frederiksberg. We obtained informed consent from all participants or their parents.

The oral glucose tolerance test was carried out in all non-diabetic patients. After an overnight fast patients were given 1·75 g glucose monohydrate/kg body weight (maximum 75 g), dissolved in 200-300 ml lemon flavoured water, to be drunk within 3-4 minutes. During the test patients rested, fasted, and did not smoke. Capillary plasma glucose concentrations were measured before, and 60 and 120 minutes after, the glucose load with a glucose dehydrogenase method (Merck).[17] According to World Health Organisation criteria, a capillary plasma glucose concentration $\leq$8·8 mmol/l at 2 hours after the glucose load is normal, 8·9-12·1 mmol/l indicates impaired glucose tolerance, and $\geq$12·2 mmol/l indicates diabetes.[18] When the test indicated diabetes we accepted the diagnosis only in patients with symptoms of hyperglycaemia (polyuria, polydipsia, and loss in weight). In patients with a diabetic test but without hyperglycaemic symptoms we repeated the test within one month in order to confirm the diagnosis. If diabetes was confirmed no further oral glucose tolerance tests were performed.

After the oral glucose tolerance test the patients' blood was sampled for measurements of glycated haemoglobin (haemoglobin A_{1c}), liver function, and precipitins against *Pseudomonas aeruginosa*. Finally, we asked the patients (or their relatives) about the daily number of pancreatic enzyme capsules that they took (as a measure of the exocrine pancreatic function) and the use of any drugs with a potential risk of influencing glucose tolerance. Measurements of haemoglobin A_{1c},[19] precipitins against *P aeruginosa*,[20] and presence of the δF508 mutation[21] were as described elsewhere. Pulmonary function was assessed monthly in all patients aged over 6 years by forced vital capacity and forced expiratory volume in one second and recorded on an electronic spirometer (Spiroton, Draeger). The results are expressed as percentages of the reference values for sex and height.[22]

STATISTICAL ANALYSIS

Statistical evaluation (with MEDSTAT statistical soft-

ware[23]) included non-parametric tests (Kruskal-Wallis, Mann-Whitney, Fisher's, and the one-tailed Page test) and life table analysis. A probability of $<0{\cdot}05$ (two-tailed) was accepted as significant.

Results

A total of 191 of the 226 patients completed the study (table I). The other 35 patients were excluded because of incomplete data: 14 had moved to other centres, 17 had fewer than five oral glucose tolerance tests, one died (from acute myelocytic leukemia), two became pregnant, and one had a heart-lung transplant. Of these 35 patients, 26 had normal glucose tolerance, two had impaired glucose tolerance, four were diabetic at their last oral glucose tolerance test, and three had unknown glucose tolerance. All but one (with impaired glucose tolerance) of the 19 patients excluded at entry because they were under 2 years old had normal glucose tolerance at the latest oral glucose tolerance test during the study period.

During the study the prevalence of diabetes increased from 11% (n=21) to 24% (n=46) in the 191 cystic fibrosis patients (fig 1), with an average annual incidence of 3·8%. In the 131 patients aged 10 or more at entry the prevalence increased from 16% (n=21) to 34% (n=44) (average annual incidence 5·0%), while in the 47 patients aged 20 or more it increased from 25% (n=12) to 53% (n=25) (average annual incidence 9.3%) (fig 1). The prevalences of normal glucose tolerance decreased from 73% (n=139) to 58% (n=110) in the total study population, from 63% (n=82) to 48% (n=63) in patients aged $\geq$10 years, and from 43% (n=20) to 38% (n=18) in patients aged $\geq$20 years (fig 1). The prevalences of impaired glucose tolerance in the total population and in patients aged $\geq$10 years were relatively stable over the five years, 15 (13-18)% and 18 (15-21)%, respectively, whereas the prevalence of impaired glucose tolerance in patients aged $\geq$20 years decreased steadily from 32% (n=15) to 9% (n=4).

DIABETES

The incidence of diabetes increased with age. No patients aged less than 10 years developed diabetes during the study. Nine of the 75 patients who did not have diabetes at the start of the study and who were aged 10-19 developed diabetes, compared with 16 of the 35 patients aged 20 years or more ($P<0{\cdot}0005$). The cumulative incidence of diabetes in the patients was 3%, 24%, and 76% at ages 10, 20, and 30 respectively (fig 2).

Of the 46 patients (25 males) who were diabetic at the end of the study, 25 (13 males) had had diabetes diagnosed during the five years. The median age at diagnosis of diabetes was 21 (range 3-40): 22 (3-40) in males and 17 (10-28) in females ($P=0{\cdot}089$) (fig 3). In 15 patients diabetes was initially suspected on clinical grounds (polyuria, polydipsia, loss in weight, or exacerbation of lung infections) and was confirmed by an oral glucose tolerance test. Two male patients, who were diabetic at the start of the study, had developed diabetes before the age of 10 (at 3 and 8 years old). They had hyperglycaemic symptoms, including ketonuria, at the time of diagnosis, and their HLA types were DR3/4 and DR4. In 31 patients without symptoms of hyperglycaemia, diabetes was indicated by the annual oral glucose tolerance test, and the diagnosis was confirmed by a second test. Another 18 asymptomatic patients' annual glucose tolerance tests indicated diabetes, but tests repeated within a month indicated normal glucose tolerance in nine patients and impaired tolerance in nine.

Seven patients developed diabetes after the start of prednisone treatment for bronchopulmonary aspergillosis, after one month to four years of prednisone. Forty diabetic patients received insulin treatment during the study (with a median (range) dose of 0·19 (0·09-2·13) IU/kg/day). At the end of the study only 34 were treated with insulin (0·33 (0·11-1·62) IU/kg/day). Four patients stopped insulin treatment because of withdrawal of prednisone, while the other two were unwilling to continue insulin treatment.

GLUCOSE TOLERANCE AND GLYCATED HAEMOGLOBIN LEVELS

At diagnosis of diabetes, the median (range) fasting plasma glucose concentration was 6·7 (4·1-9·0) mmol/l and the median haemoglobin A_{1c} level was 5·8%

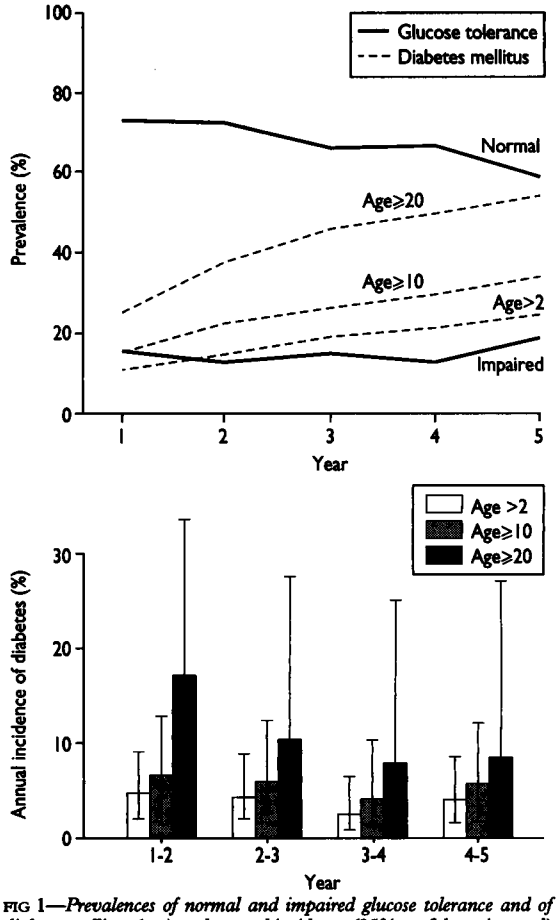

FIG 1—*Prevalences of normal and impaired glucose tolerance and of diabetes mellitus (top) and annual incidence (95% confidence interval) of diabetes mellitus (bottom) in 191 cystic fibrosis patients aged over 2 years. (Prevalence and incidence of diabetes are given for total study population (age >2 years) and for patients aged ≥10 and ≥20 years)*

TABLE I—*Clinical data at entry for 191 patients with cystic fibrosis, who were classified according to WHO criteria of glucose tolerance.[18] (Values are medians (ranges) unless stated otherwise)*

	Glucose tolerance			
	Normal	Impaired	Diabetes mellitus	Total
No of patients (males:females) (% of total)	139 (74:65) (73)	31 (11:20) (16)	21 (12:9) (11)	191 (97/94)
No of patients with each cystic fibrosis genotype*	108:27:4:0	21:10:0:0	16:4:0:1	145:41:4:1
Age (years)	11·5 (2-38)	19·3 (5-32)	20·3 (14-40)	13·6 (2-40)
Body mass index (kg/m²)	16·5 (12·9-23·9)	18·1 (13·8-25·3)	19·7 (16·8-23·3)	17·1 (12·9-25·3)
Forced expiratory volume in 1 second (% of normal)†	69 (20-118)	55 (24-121)	52 (27-99)	65 (20-121)
Forced vital capacity (% of normal)†	90 (39-140)	79 (44-136)	82 (50-112)	86 (39-140)
No (%) of patients in group with pseudomonas infection	78 (56)	25 (81)	17 (81)	120 (63)
No of pseudomonas precipitins	1 (0-48)	23 (0-45)	30 (0-43)	5 (0-48)
No of pancreatic enzyme capsules taken daily	30 (0-211)	30 (0-137)	27 (0-109)	30 (0-211)
Haemoglobin A_{1c} level (%)‡	5·2 (4·1-6·2)	5·7 (4·9-7·1)	6·1 (5·2-11·8)	5·4 (4·1-11·8)

*Genotypes δF508/δF508: δF508/other: Other/other: Not detected.
†Data taken from 106 patients with normal glucose tolerance and 30 with impaired glucose tolerance, all more than 6 years old.
‡Normal range 4·1-6·4%.[19]

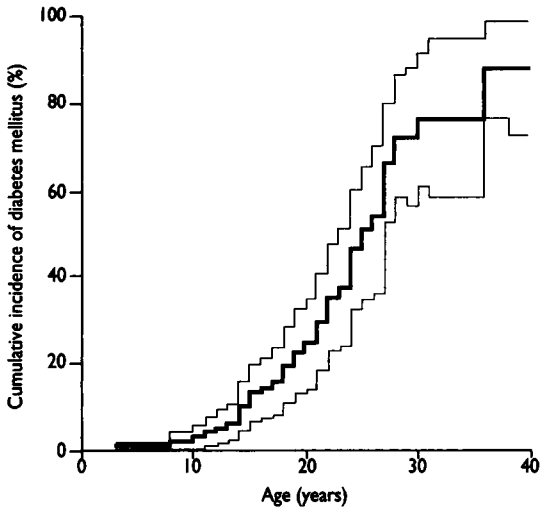

FIG 2—*Cumulative incidence (95% confidence interval) of diabetes mellitus in patients with cystic fibrosis based on life table analysis with 191 patients, including 46 diabetics*

(4·8-9·3%). Of the 25 patients who had diabetes diagnosed during the study, four had fasting plasma glucose concentrations above the upper normal limit of 7·8 mmol/l[18] and four had haemoglobin A_{1c} levels above the upper normal limit of 6·4%. Eight patients with normal glucose tolerance and two with impaired glucose tolerance had fasting plasma glucose concentrations $\geq$7·8 mmol/l; two of these patients with normal glucose tolerance and one with impaired glucose tolerance developed diabetes during the study. Two patients with normal glucose tolerance and two with impaired glucose tolerance had haemoglobin A_{1c} levels >6·4%; both of the patients with impaired glucose tolerance developed diabetes during the study. Table II shows predictive values and odds ratios for impaired glucose tolerance, fasting hyperglycaemia, and haemoglobin A_{1c} levels above the upper normal limit.

A total of 640 glucose tolerance tests were classified as normal, and 143 indicated impaired glucose tolerance. The corresponding figures for patients aged 10 or more were 376 and 115, and those for patients aged 20 or more were 96 and 40. No patient had impaired glucose tolerance at all tests, but 95 patients had impaired glucose tolerance at least once during the study, including 21 of the 25 patients who developed diabetes during the study. Of the 108 cases of impaired glucose tolerance found during the first four years of the study, the following oral glucose tolerance test indicated normal tolerance in 63 cases, impaired tolerance in 30 cases, and diabetes in 15 cases.

Only 71 patients had normal glucose tolerance at all five tests during the study. In these patients fasting plasma glucose concentrations increased insidiously during the study from 5·2 mmol/l to 5·6 mmol/l, as did plasma glucose concentrations after glucose loading, from 5·9 mmol/l to 6·3 mmol/l, and haemoglobin A_{1c} levels, from 5·1% to 5·4 % (table III). Throughout the study haemoglobin A_{1c} levels were lower in the 71 patients with normal glucose tolerance at all tests (overall median level 5·2% (range 3·7-6·5%)) than in the 74 patients with variable glucose tolerance (normal or impaired, but not indicating diabetes) (overall level 5·3% (3·2-6·5%)), in the 25 patients who developed diabetes during the study (5·8% (4·1-11·0%)), and in the 21 patients who had diabetes at entry (6·5% (4·8-13·9%)) ($P<0·00001$).

TABLE II—*Positive and negative predictive values (95% confidence intervals) and odds ratios for impaired glucose tolerance measured in previous years and for increased fasting plasma glucose concentrations and haemoglobin A_{1c} levels measured on day of oral glucose tolerance test in diagnosing diabetes mellitus in cystic fibrosis*

	Impaired glucose tolerance	Fasting plasma glucose concentrations $\geq$7·8 mmol/l	Haemoglobin A_{1c} level >6·4%
	Patients aged >2 years		
Predictive value (%):			
Positive	16 (9 to 24)	33 (11 to 62)	50 (18 to 82)
Negative	97 (95 to 98)	96 (94 to 98)	96 (94 to 98)
Odds ratio	5·6	8·7	13·0
	Patients aged $\geq$10 years		
Predictive value (%):			
Positive	15 (9 to 25)	33 (10 to 65)	56 (21 to 98)
Negative	95 (92 to 97)	94 (92 to 97)	94 (91 to 97)
Odds ratio	3·2	5·9	9·9
	Patients aged $\geq$20 years		
Predictive value (%):			
Positive	25 (12 to 42)	50 (7 to 94)	40 (5 to 86)
Negative	92 (84 to 97)	89 (82 to 94)	89 (82 to 94)
Odds ratio	3·3	4·5	3·5

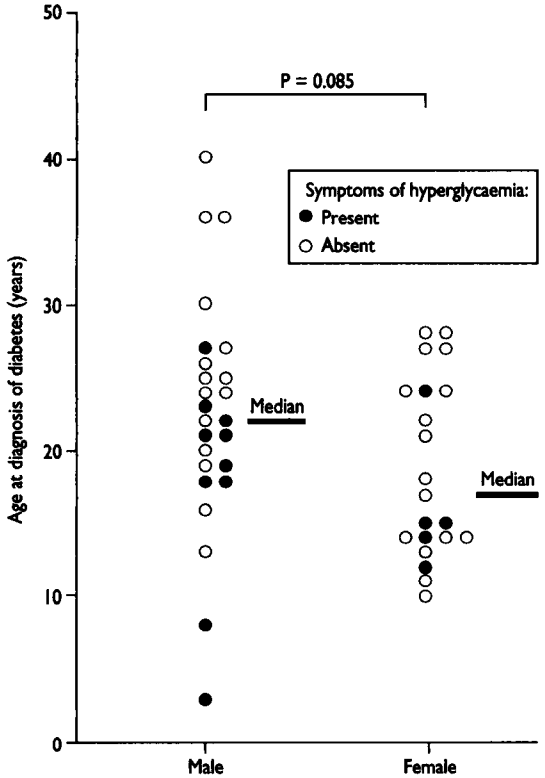

FIG 3—*Age and symptoms of hyperglycaemia at diagnosis of diabetes mellitus in 25 male and 21 female patients with cystic fibrosis*

Discussion

In our study the patients had a median age of 13·6 years, and during the study the prevalence of glucose intolerance (impaired tolerance and tolerance indicating diabetes) increased from 27% to 42% and the prevalence of diabetes had increased from 11% to 24%. The annual incidence of diabetes was relatively constant, averaging 3·8% a year in the total population, and increased with age: 5·0% a year in patients aged 10 or more and 9·3% a year in patients aged 20 or more. Arrigo *et al* studied 32 patients with cystic fibrosis (mean age 12·8 years) who underwent oral glucose tolerance tests on two occasions two years apart.[24] In their study the prevalence of glucose intolerance (impaired tolerance and tolerance indicating diabetes, WHO criteria[18]) increased from 37·5% to 50%. Two patients developed diabetes, corresponding to an incidence of 3% a year (confidence interval 1% to 21%). To our knowledge no other longitudinal studies of the incidence of diabetes in cystic fibrosis exist.

It is unknown whether the presence of diabetes affects survival of patients with cystic fibrosis.[1,2,25]

TABLE III—*Fasting plasma glucose concentrations, plasma glucose concentrations after glucose loading, and haemoglobin A_{1c} levels in 71 cystic fibrosis patients with normal glucose tolerance by oral glucose tolerance test for five consecutive years. (Values are medians (ranges) unless stated otherwise)*

	Year					P value of Page test
	1	2	3	4	5	
Fasting plasma glucose concentration (mmol/l)	5·2 (3·8-9·1)	5·5 (3·5-9·8)	5·4 (3·4-7·3)	5·7 (3·5-6·6)	5·6 (3·8-7·4)	<0·00005
Plasma glucose concentration after glucose loading (mmol/l)	5·9 (2·5-8·6)	5·7 (3·1-8·7)	6·2 (2·7-8·7)	6·6 (2·5-8·4)	6·3 (3·4-8·7)	<0·05
Haemoglobin A_{1c} level (%)*	5·1 (4·1-6·0)	5·0 (3·7-6·3)	5·1 (4·1-5·9)	5·3 (4·3-6·2)	5·4 (3·8-6·4)	<0·00001

*Normal range 4·1-6·4%.[19]

There is evidence, however, that the overall clinical status deteriorates gradually in diabetic[1 6] and prediabetic[26] patients with cystic fibrosis compared with non-diabetic patients and that insulin treatment of diabetic patients improves lung function and reduces the number of lung infections with *Haemophilus influenzae* and *Streptococcus pneumoniae*.[27] Moreover, diabetic patients with cystic fibrosis are probably no less prone to developing late diabetic complications than are patients with other types of diabetes of similar duration and glycaemic control.[8] It is therefore important to diagnose and treat diabetes in patients with cystic fibrosis and to identify those patients at risk of developing diabetes.

IDENTIFICATION

Since diabetes in cystic fibrosis is often asymptomatic (67% of newly diagnosed patients in our study), it is often underdiagnosed. Thus, the reported prevalences of diabetes requiring insulin treatment of 4·1% and 5·2% in large groups of American (median age 12·5 years)[5] and Canadian (mean age 17·3)[2] cystic fibrosis patients were lower than would have been expected from our findings: prevalences of diabetes of 11% at entry (median age 13·5) and 24% at exit (median age 17·3). Only 16% of our diabetic patients had abnormally high fasting plasma glucose concentrations ($\geq$7·8 mmol/l)[18] and haemoglobin A_{1c} levels (>6·4%) at the time of diagnosis of diabetes. Regular oral glucose tolerance tests are therefore mandatory to diagnose diabetes. We suggest that annual oral glucose tolerance tests are started as part of clinical practice in cystic fibrosis patients over the age of 10, as our two patients who developed diabetes below this age both had frank symptoms of diabetes at onset.

Identifying cystic fibrosis patients who are at risk of diabetes is desirable. As in non-insulin dependent diabetes,[9 18] impaired glucose tolerance seems to be a risk marker for the development of diabetes in cystic fibrosis, with an age dependent odds ratio of 3-6 compared with normal glucose tolerance, and 21 of the 25 patients who developed diabetes during the study had impaired glucose tolerance at least once. However, since 58% of the tests that showed impaired glucose tolerance were followed the next year by tests showing normal tolerance (in accordance with the rate of reversion of impaired to normal glucose tolerance of 28-67% reported elsewhere[9]), the presence of impaired glucose tolerance is not a reliable predictor of diabetes in cystic fibrosis. From this and previous studies we can therefore conclude that cystic fibrosis patients at risk of developing diabetes cannot be reliably identified by the presence of impaired glucose tolerance, fasting hyperglycaemia, haemoglobin A_{1c} levels above the upper normal limit, residual β cell function,[28] cystic fibrosis genotype[29] (though exocrine pancreatic insufficiency may have to be present for diabetes to develop in cystic fibrosis[30-32]), HLA type,[33] presence of islet cell cytoplasmic antibodies,[24 33] or family history of diabetes.[24 33 34]

Only 37% of our patients were classified as normal at all five oral glucose tolerance tests. Within this group of patients plasma glucose concentrations, after both fasting and glucose loading, and haemoglobin A_{1c} levels increased insidiously, supporting the theory that β cell function deteriorates progressively in cystic fibrosis patients.

Key messages

- As life span of patients with cystic fibrosis has increased, diabetes mellitus has evolved as a common complication
- In this five year study of patients with cystic fibrosis we performed annual glucose tolerance tests and found cumulative incidence of diabetes of 24% in patients aged 20 and 76% in those aged 30
- Since diabetes in cystic fibrosis is associated with deterioration in overall clinical status and since late diabetic complications may develop, these patients should be identified
- Presence of hyperglycaemic symptoms, fasting hyperglycaemia, and increased levels of glycated haemoglobin did not reliably identify diabetes mellitus in patients with cystic fibrosis
- Annual screening with oral glucose tolerance test is therefore recommended for all cystic fibrosis patients aged over 10

PATHOGENESIS

The reason for the development of diabetes in cystic fibrosis is not fully understood. In cystic fibrosis patients who are not diabetic but have exocrine pancreatic insufficiency the number of islets of Langerhans is normal or slightly reduced,[35] but in cystic fibrosis patients with diabetes the number of islets and β cells are reduced by 30-50%.[35-37] The configuration of the islets is altered so that they exist in disorganised clusters separated by broad bands of fibrous tissue and fatty replacement and degeneration,[6 35-37] which, together with impairment of blood supply, may contribute to the abnormal endocrine function. Since the discovery and cloning of the cystic fibrosis transmembrane regulator gene it has been possible to search for its expression at the mRNA and gene product levels in various tissues. Its mRNA is present in the centroacinar cells of the intercalated duct of the pancreas but not in the surrounding serous acini or in the islets of Langerhans.[38] Correspondingly, the major mutation genotype in cystic fibrosis (δF508) affects the severity of the exocrine pancreatic insufficiency, whereas the endocrine pancreatic function is unrelated to this genotype.[29]

CONCLUSION

Our longitudinal study of unselected cystic fibrosis patients has shown that glucose tolerance deteriorates gradually, with an age dependent annual incidence of diabetes of 4-9%, which resulted in a doubling of the prevalence of diabetes to 24% within five years. Cystic fibrosis patients at risk of diabetes cannot be identified with certainty, although patients with impaired glucose tolerance are at higher risk than patients with normal glucose tolerance. Since all cystic fibrosis patients with diabetes cannot be identified by the presence of hyperglycaemic symptoms, increased fasting plasma glucose concentrations, or increased haemoglobin A_{1c} levels, we recommend that annual oral glucose tolerance tests be carried out in all cystic fibrosis patients over the age of 10.

We thank the staff at the CF Department 5063, Rigshospitalet, for their skilled assistance.

Funding: None.

Conflict of interest: None.

1 Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu S-C, *et al.* Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;112: 373-7.
2 Reisman J, Corey M, Canny G, Levison H. Diabetes mellitus in patients with cystic fibrosis: effect on survival. *Pediatrics* 1990;150:374-7.
3 Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;46:881-5.
4 Nir M, Lanng S, Koch C. Long-term survival and nutritional data in Danish centre-treated cystic fibrosis patients. *Thorax* (in press).
5 FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993;122:1-9.
6 Handwerger S, Roth J, Gorden P, Di Sant'Agnese P, Carpenter DF, Peter G. Glucose intolerance in cystic fibrosis. *N Engl J Med* 1969;281:451-61.
7 Lanng S, Thorsteinsson B, Erichsen G, Nerup J, Koch C. Glucose tolerance in cystic fibrosis. *Arch Dis Child* 1991;66:612-6.
8 Lanng S, Thorsteinsson B, Lund-Andersen C, Nerup J, Schiøtz PO, Koch C. Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications. *Acta Paediatr* 1994;83:72-7.
9 Yudkin JS, Alberti KGMM, McLarty DG, Swai ABM. Impaired glucose tolerance. Is it a risk factor for diabetes or a diagnostic ragbag? *BMJ* 1990;301:397-402.
10 Little RR, England JD, Wiedmeyer HM, Madsen RW, Pettitt DJ, Knowler WC, *et al.* Glycated haemoglobin predicts progression to diabetes mellitus in Pima Indians with impaired glucose tolerance. *Diabetologia* 1994;37:252-6.
11 Artal R, Mosley GM, Dorey FJ. Glycohemoglobin as a screening test for gestational diabetes. *Am J Obstet Gynecol* 1984;148:412-4.
12 Bank S, Marks IN, Vinik AI. Clinical and hormonal aspects of pancreatic diabetes. *Am J Gastroenterol* 1975;64:13-22.
13 Bistritzer T, Sack J, Eshkol A, Katznelson D. Hemoglobin A_1 and pancreatic β cell function in cystic fibrosis. *Isr J Med Sci* 1983;19:600-3.
14 Stutchfield PR, O'Halloran S, Teale JD, Isherwood D, Smith CS, Heaf D. Glycosylated haemoglobin and glucose intolerance in cystic fibrosis. *Arch Dis Child* 1987;62:805-10.
15 Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959;23:545-9.
16 Nielsen OH, Flensborg EW. Sweat electrolyte investigation by Gibson and Cooke's pilocarpine iontophoresis method. *Ugeskr Laeger* 1981;143:2302-6.
17 Banauch D, Brümmer W, Ebeling W, Metz H, Rindfrey H, Lang H, *et al.* A glucose dehydrogenase for the determination of glucose concentration in body fluids. *Zeitschrift für Klinische Chemie und Klinische Biochemie* 1975;13: 101-7.
18 WHO Study Group. Diabetes mellitus. *WHO Technical Report Series* 1985;727:1-113.
19 Svendsen PA, Lauritzen T, Søegaard U, Nerup J. Glycosylated haemoglobin and steady state mean blood glucose concentration in type 1 (insulin-dependent) diabetes. *Diabetologia* 1982;23:403-5.
20 Høiby N. Pseudomonas aeruginosa infection in cystic fibrosis. Diagnostic and prognostic significance of Pseudomonas aeruginosa precipitins determined by means of crossed immunoelectrophoresis. A survey. *Acta Pathologica et Microbiologica Scandinavica. Section C, Immunology* 1977;85(suppl 262): 3-96.
21 Schwartz M, Johansen HK, Koch C, Brandt NJ. Frequency of the δF508 mutation on cystic fibrosis chromosomes in Denmark. *Hum Genet* 1990;85: 427-8.
22 Polgar G, Promadhat V. *Pulmonary function testing in children: techniques and standards.* Philadelphia: WB Saunders, 1971:88-107, 178-82.
23 Wulff HR, Schlichting P. *MEDSTAT, version 2.* Albertslund, Denmark: Astra-Gruppen A/S, 1988.
24 Arrigo T, Cucinotta D, Conti Nibali S, Di Cesare E, Di Benedetto A, Magazzù G, *et al.* Longitudinal evaluation of glucose tolerance and insulin secretion in non-diabetic children and adolescents with cystic fibrosis: results of a two-year follow-up. *Acta Paediatr* 1993;82:249-53.
25 Rodman HM, Doershuk CF, Roland JM. The interaction of 2 diseases: diabetes mellitus and cystic fibrosis. *Medicine* 1986;65:389-97.
26 Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Pediatr* 1992;151:684-7.
27 Lanng S, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr* 1994;83:849-53.
28 Lanng S, Thorsteinsson B, Røder ME, Ørskov C, Holst JJ, Nerup J, *et al.* Pancreas and gut hormone responses to oral glucose and intravenous glucagon in cystic fibrosis patients with normal, impaired, and diabetic glucose tolerance. *Acta Endocrinol* 1993;128:207-14.
29 Lanng S, Schwartz M, Thorsteinsson B, Koch C. Endocrine and exocrine pancreatic function and the δF508 mutation in cystic fibrosis. *Clin Genet* 1991;40:345-8.
30 Geffner ME, Lippe BM, Kaplan SA, Itami RM, Gillard BK, Levin SR, *et al.* Carbohydrate tolerance in cystic fibrosis is closely linked to pancreatic exocrine function. *Pediatr Res* 1984;18:1107-11.
31 Lamers CBHW, Jansen JBMJ, Hafkenscheid JCM, Jongerius CM. Evaluation of tests of exocrine and endocrine pancreatic function in older patients with cystic fibrosis. *Pancreas* 1990;5:65-9.
32 Moran A, Diem P, Klein DJ, Levitt MD, Robertson RP. Pancreatic endocrine function in cystic fibrosis. *J Pediatr* 1991;118:715-23.
33 Lanng S, Thorsteinsson B, Pocoit F, Marshall MO, Madsen HO, Schwartz M, *et al.* Diabetes mellitus in cystic fibrosis: genetic and immunological markers. *Acta Paediatr* 1993;82:150-4.
34 Robert JJ, Grasset E, De Montalembert M, Chevenne D, Deschamps I, Boitard C, *et al.* Recherche de facteurs d'intolérance au glucose dans la mucoviscidose. *Arch Fr Pediatr* 1992;49:17-22.
35 Abdul-Karim FW, Dahms BB, Velasco ME, Rodman HM. Islets of Langerhans in adolescents and adults with cystic fibrosis. *Arch Pathol Lab Med* 1986;110:602-6.
36 Iannucci A, Mukai K, Johnson D, Burke B. Endocrine pancreas in cystic fibrosis: an immunohistochemical study. *Hum Pathol* 1984;15:278-84.
37 Soijima K, Landing BH. Pancreatic islets in older patients with cystic fibrosis with and without diabetes mellitus: morphometric and immunocytologic studies. *Pediatr Pathol* 1986;6:25-46.
38 Trezise AEO, Buchwald M. In vivo cell-specific expression of the cystic fibrosis transmembrane conductance regulator. *Nature* 1991;353:434-7.

(Accepted 26 June 1995)

Ethics approval for a national postal survey: recent experience

Claire Middle, Ann Johnson, Tracey Petty, Lois Sims, Alison Macfarlane

National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE
Claire Middle, *survey researcher*
Ann Johnson, *developmental paediatrician*
Tracey Petty, *administrator*
Lois Sims, *programmer*
Alison Macfarlane, *medical statistician*

Correspondence to:
Dr Macfarlane.

BMJ 1995;311:659-60

Before any study can be done on a national scale, permission must be sought from a large number of local ethics committees. We describe the resources required and the problems and issues that arose when we sought approval from ethics committee for a national postal survey in England and Wales.

Methods and results

We wanted to mount a postal survey in all parts of England and Wales of a national sample of children who were born in 1988 and were stratified by birth weight. After identifying the children from birth registration and tracing them through the NHS central register, we planned to send self administered questionnaires to the children's parents, general practitioners, and teachers. We identified 162 local research ethics committees in England and Wales from the *Medical Research Ethics Committees Directory*.[1] Each was sent a letter outlining the project and asking how an application should be made.

Seventeen committees told us that it was not appropriate to apply to them for ethics approval for this study; the remainder needed some type of formal application. Thirteen committees did not have a specific application form but requested between one copy and 21 copies of the protocol. Of the 132 committees that used an application form, 118 had a unique form, ranging in length from two to 18 pages. In the former Northern region a single application was considered by a "lead" committee on behalf of the seven others. In the former South Western region an application followed a standard format but each committee considered it separately. Seventy six committees requested 10 or more copies of the completed application form and protocols.

In all, we sent a total of 1095 protocols and 1116 application forms, together with a number of supporting documents. We estimated that, in total, this required seven to eight weeks of staff time. The cost of staff time, photocopying, and postage was estimated to be £4606, an average of £32 for each committee. This does not include the costs and time spent on additional telephone calls to clarify issues, responses to requests for additional information, and setting up and maintaining a database to record details of correspondence.

Three months after submitting applications to the 145 committees, 113 had responded. Eighty two expressed no objection to the study. Others raised a number of issues, including concerns about the aims of the study, its cost, confidentiality, consent, and the wording of the questionnaires and information sheets. Thirty one requested resubmission.

Comment

Seeking approval for a study covering a large geographical area is time consuming and expensive for both researchers and ethics committees. Researchers