Long term survival and nutritional data in patients with cystic fibrosis treated in a Danish centre

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Abstract

Background – Adequate nutrition and optimal treatment of bronchopulmonary infections are both of critical importance in maintaining the health of patients with cystic fibrosis. The cystic fibrosis centre in Copenhagen has followed a regimen of very early and aggressive antimicrobial treatment, especially against *Pseudomonas aeruginosa* infection. An unrestricted diet of low fat and high protein without hyperalimentation was recommended before 1985 which was then changed to a high fat, high calorie intake.
Methods – The overall impact of the treatment regimen was evaluated by a cross sectional analysis of all 223 patients who attended the centre in 1989. Growth and nutritional parameters were combined with lung function parameters and with a retrospective analysis of chronic *P aeruginosa* infection and its duration. Survival curves for all 313 patients treated at the centre since 1949 were calculated.
Results – All the patients with cystic fibrosis had normal height, although the final height was achieved a little later than in healthy controls. Body weight was lower than normal in males above 15 and in females above 10 years of age. The body mass index (BMI), which was approximately 98% of normal in the younger patients, declined to 90% in adult men and to 83% in adult women with cystic fibrosis, and was strongly correlated with lung function parameters. In 1989 the median age of survival of all patients treated in the centre since 1949 was 30 years (32 years in males and 29 years in females).
Conclusions – The overall treatment regimen in the cystic fibrosis centre in Copenhagen is associated with growth and survival rates that are at least equal to those in other cystic fibrosis centres in other countries.
(*Thorax* 1996;51:1023–1027)

Keywords: cystic fibrosis, survival, nutrition.

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Nutritional recommendations for patients with cystic fibrosis differ among centres, with most recommending a high fat, high calorie diet.[1] This is supplemented in some centres by hyperalimentation through nasogastric[1-3] gastrostomy/jejunostomy tubes,[1-9] and occasionally with parenteral nutrition.[1] However, there is disagreement as to the effect of these procedures on lung function and on the prognosis.[1-11]

Corey *et al* in a comparative study between patients with cystic fibrosis in Toronto and Boston[12] concluded that the longer survival of the patients in Toronto was due mainly to better nutritional status as a result of hyperalimentation, as lung function was similar in the two groups.

At the cystic fibrosis centre in Copenhagen a low fat, high protein diet was recommended until 1985, after which the diet became unrestricted and a high fat, high calorie diet is now recommended comprising 100–150% of the total calorie intake recommended by the World Health Organisation for healthy persons. The calorie intake is distributed as 40% fat, 20% protein, and 40% carbohydrates. Individual food intake is supplemented by an amount of pancreatic enzymes that allows normal height and weight gain and no steatorrhoea. Moreover, the treatment regimen includes rigorous control of infection and aggressive antimicrobial treatment.[13 14] Briefly, specimens of lower respiratory tract secretions are obtained by expectoration or nasolaryngeal suction at least once every month on a regular basis in all patients as well as at clinic visits in between the monthly visits because of acute signs or symptoms of infection. Peroral antimicrobial chemotherapy is instituted for 14 days whenever pathogenic bacteria are identified by microscopy and culture according to fixed protocols, even in the absence of signs or symptoms of lower respiratory tract infection.[13] In addition, since 1975–6 elective 14 day courses of intravenous antipseudomonas chemotherapy have been administered approximately every third month to all patients with chronic *P aeruginosa* infection, usually a combination of tobramycin and a suitable beta-lactam antibiotic.[13 14] In unstable patients the intervals between courses may be shortened and/or oral quinolones may be given and, since 1987, all patients chronically infected with *P aeruginosa* have taken regular inhalations of colistin twice daily.

In this retrospective study we have tried to evaluate the impact of major changes in nutrition and in antimicrobial treatment over several decades in the hope of adding some information on these issues.

Methods

The study period for the cross sectional investigation of growth parameters was the whole

of 1989 and the population studied comprised all 223 patients (115 males) with cystic fibrosis attending the centre during this period. All were treated entirely at the centre and many from the time of diagnosis. The mean age of the patients was 14.9 years (range 4 months to 41 years) with no difference between males and females. The patients were seen monthly in the outpatient clinic, and each visit included measurement of lung function by spirometric tests, height and weight, and bacteriological investigation of lower respiratory tract secretions.[13 14] The number of capsules of entero-soluble microspheres (Pancrease, Cilag, Denmark) taken per meal was recorded. Values were standardised as per m^2 of body surface and per kg body weight.

GROWTH PARAMETERS
The growth parameters used were the height and weight standard deviation scores (HSDS, WSDS), also called Z scores, and the body mass index (BMI).

The HSDS and WSDS were determined as actual height or weight minus the median normal height or weight for age and sex divided by SD for age and sex. The actual height and weight were median values of at least six measurements during the year of the study. The median values of height and weight and SD in healthy Danish children up to 18 years of age were derived from tables,[15] whereas the corresponding values for adults were from a recent study of a large unselected group of normal inhabitants in the Copenhagen area conducted between 1981 and 1983.[16]

The BMI in patients below 19 years was calculated as actual log weight (kg) − 0.0008 × height $(cm)^{17}$ and expressed as a percentage of the BMI calculated from the tables for median height and weight in Danish children.[15] In patients older than 18 years the BMI was calculated as actual weight/height^2 and expressed as a percentage of the median BMI in healthy Danish men and women.[16]

PULMONARY FUNCTION
The median values of at least six recordings during the study period of forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC) expressed as a percentage of predicted values for height and sex[18] were used.

SURVIVAL ANALYSIS
To determine the median survival of the patients life table analysis was performed on all patients with cystic fibrosis born without meconium ileus who attended the cystic fibrosis centre from 1949 to December 1989. Three hundred and thirteen patients (163 men) were included in the survival analysis, 221 of whom were still alive on 31 December 1989. Twenty six patients with meconium ileus at birth and two who died from complications following premature birth were not included in the survival analysis to allow a comparison to be made with published analyses of survival from other

centres which have also excluded patients born with meconium ileus.

INFECTIONS
The onset of chronic *P aeruginosa* infection was defined as a positive culture in the lower respiratory tract secretions at each of six consecutive visits or for a shorter time but with a significant increase in specific anti-*P aeruginosa* serum antibodies.

The genotyping was performed as described previously.[19]

DATA ANALYSIS
The 5% level of significance was chosen (two-tailed). To estimate correlations between the variables the Spearman rank correlation test was used. Data were compared using the Fisher exact test and unpaired *t* tests. For comparison of two groups the Mann-Whitney test was used. Survival rates were calculated by the life table method (log rank analysis).

Results
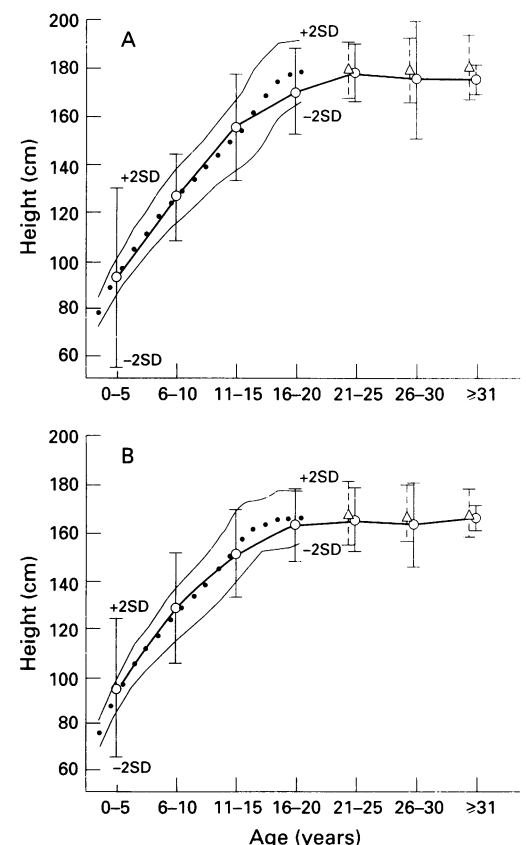The overall median height of both male and female patients was 0.46 SD below normal

Figure 1 Height of (A) 115 Danish males and (B) 108 females with cystic fibrosis (median (O ± 2SD) in five year age groups. The median height (●) ± 2SD of normal Danish males and females until age 18 is shown for each year, and the median height (△) ± 2SD of normal males and females aged between 20 and 40 years in five year age groups. The numbers of males with cystic fibrosis in each age group beginning with the youngest are: 17, 20, 21, 24, 17, 9, and 7, and the numbers of females are 19, 19, 27, 18, 13, 10, and 2.
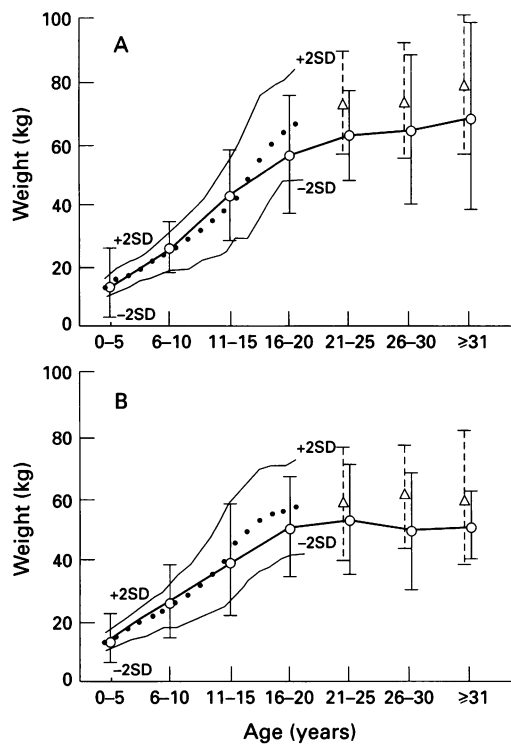
Figure 2 Weight of (A) 115 Danish males and (B) 108 females with cystic fibrosis (median (O) ±2SD) in five year age groups compared with the median weight (●) ±2SD of normal Danish males and females. Symbols and numbers of patients in each age group as for fig 1.
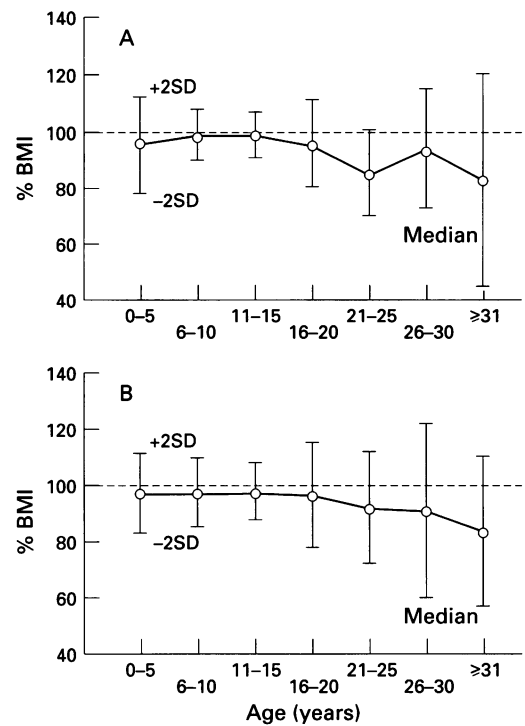

Figure 3 Body mass index (BMI) of (A) 115 Danish males and (B) 108 Danish females with cystic fibrosis as a percentage of the BMI of normal Danish males and females (median (O) ±2SD). The numbers of patients in each group are as for fig 1.

average whereas overall weight was 0.60 SD below normal average in males and 0.70 SD in females. The overall median BMI, which provided a good estimate of weight for height, was 96% of normal median BMI.

Figure 1 shows the actual heights of the patients with cystic fibrosis compared with the height of normal Danish males and females in relation to their age. The heights of both males and females with cystic fibrosis were similar to the normal Danish population. However, the number of females older than 30 years was too small for statistical comparison. The final heights of both men and women with cystic fibrosis are reached later than in controls, although this delay also did not reach statistical significance.

Figure 2 shows the weight of the patients in relation to age, together with the median weight of normal Danish males and females. Boys aged 0–5 years with cystic fibrosis were heavier than their normal counterparts (mean body weight 13.3 kg versus 12.5 kg, p <0.05), but the body weight of boys with cystic fibrosis in the 6–10 and 11–15 year age groups did not differ significantly from those of normal boys of the same age (fig 2A). However, above the age of 15 years males with cystic fibrosis were significantly lighter than their normal counterparts (p <0.0005 for the 16–25 age group, p <0.05 for those aged 26–30, and p <0.005 for men above 30 years). The pattern for girls with cystic fibrosis (fig 2B) was the same as for the boys but the decline in weight began after the age of 10. Girls with cystic fibrosis aged 0–5 years were heavier than normal Danish girls (p <0.0005), but the weight in the 6–10

age group was the same as normal. Above 10 years girls and women with cystic fibrosis were lighter than normal (p <0.001 for the 11–20 age group, p <0.005 for those aged 21–25 years, and p <0.001 for those in the 26–30 age group).

The median BMI as a percentage of the BMI of the normal Danish population matched for age and sex is shown in fig 3. The BMI was close to normal until age 20 in patients with cystic fibrosis of both sexes whereafter it declined to about 90% of normal in men with cystic fibrosis and to approximately 80% in women. After the age of 30 years this decline was a result of increasingly lower weights in the adult patients who attained normal height.

As the figures only show median values of height and weight with the possibility of hiding the lightest and shortest of our patients, we looked specifically at those most growth retarded – that is, below the third percentile (–1.88 SD) of the normal population. They comprised 10% of males and females for height, and 9% of males and 8% of females for weight. However, 28% of males and 30% of females were higher than the 50th percentile of the normal Danish population and 27% of males and 26% of females were heavier.

Table 1 shows correlations between the BMI and key parameters influencing the clinical status of our patients. BMI declined significantly with age for both male and female patients and with the duration of chronic P aeruginosa infection in males. There was a strong positive correlation between the BMI and dynamic lung function parameters: FEV$_1$% (R = 0.52 in males and 0.55 in females, p <0.0001) and

Table 1   Correlation between body mass index (BMI) and key clinical parameters in Danish patients with cystic fibrosis

	Males		Females	
	R	p*	R	p*
Age	−0.3491	0.0005	−0.2808	0.005
Duration of chronic P aeruginosa infection**	−0.2460	<0.01	−0.1765	NS
FEV₁%***	0.5201	<0.0001	0.5450	<0.0001
FVC%***	0.4065	0.0001	0.4867	<0.0001

*Spearman rank correlation test.
**Chronic *P aeruginosa* infection was present in 138 patients (74 males (62%)) with a mean duration of nine years (range 0.3–24). The age at onset of the infection was 15 months to 30 years (median 10 years).
***Determined in 173 patients (89 males (51%)) aged 7–41 years (median 18). Median (SD) forced vital capacity (FVC) was 85 (23)% of predicted and forced expiratory volume in one second (FEV_1) was 65 (24)%. FEV_1, but not FVC, was significantly lower in patients infected with *P aeruginosa* than in those not infected (60% versus 76%, p <0.0005, Mann-Whitney test). Neither FEV_1 nor FVC correlated with the duration of chronic *P aeruginosa* infection.
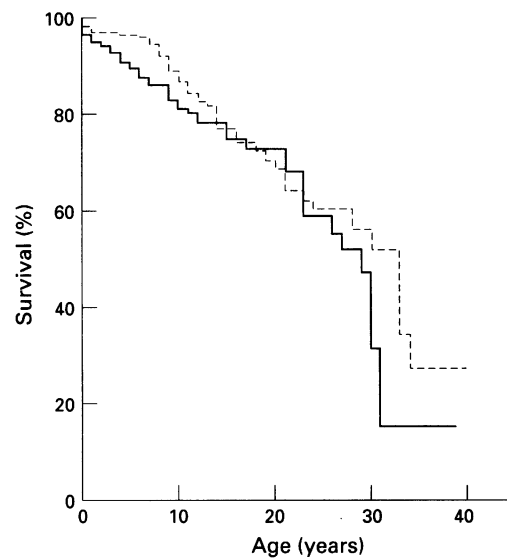

Figure 4   Survival of 163 male (------) and 150 female (——) patients with cystic fibrosis born without meconium ileus in the period 1948–89.

FVC% (R = 0.41, p = 0.0001 in males, R = 0.49, p <0.0001 in females).

There was no correlation between BMI and pancreatic insufficiency as determined by the number of Pancrease capsules supplemented per m^2 of body surface per meal (0–48 capsules, median 8.3) or per kg of body weight per meal (0–1.9 capsules, median 0.27). The BMI did not correlate with the DNA type expressed as homozygosity/heterozygosity for the ΔF508 mutation in 218 of the patients (172 patients (79%) were homozygous and 46 (20%) heterozygous). The number of Pancrease capsules used correlated strongly with the DNA type (p <0.0002 for number of capsules per m^2/meal and p <0.0004 per kg/meal, Mann-Whitney test).

In 1989 the median survival was 30 years for all patients born without meconium ileus. No sex differences in survival were detected, with the median survival being 29 years for females and 32 for males (fig 4). The median age of survival did not change if the 26 patients born with meconium ileus between 1949 and 1989 were included.

Discussion

This cross sectional study of growth and survival of Danish patients with cystic fibrosis who were receiving a normal unrestricted diet without hyperalimentation revealed normal height in all age groups and normal weight and BMI in prepubertal patients, but below normal weight in adolescents and adults. The percentage of growth retarded patients (below the third percentile) was similar to that published from Toronto[12] and lower than that reported from Australia.[20] Low weight and BMI were both clearly related to age (figs 2 and 3).

The median survival rates are similar to the best survival results published from other big cystic fibrosis centres[12 21] and seven years more than that of patients treated in our centre between 1970 and 1981.[22] The shape of the overall survival curves (fig 4) clearly demonstrates an excess mortality in older patients.

Our treatment policy was fairly uniform until around 1975. In 1976 the treatment of chronic *P aeruginosa* lung infection was changed from treating acute exacerbations only to regular intravenous chemotherapy four times per year with a subsequent significant decrease in mortality in *P aeruginosa* infected patients.[23 24] Furthermore, a decrease in the incidence of chronic *P aeruginosa* infection followed segregation of infected and non-infected patients after 1981[25] and the introduction some years later of early treatment of *P aeruginosa* colonisation.[26] In 1985 the previously recommended low fat diet was abolished and a high calorie, high fat diet was recommended.

The data on weight, BMI, and survival in relation to age indicate that poor growth and excess mortality are predominantly features of older patients. Both could be related to inadequate anti-pseudomonas treatment before 1976 as well as to poor nutrition before 1985. The immediate decrease in annual mortality after changing to a more aggressive anti-pseudomonas treatment regimen in 1976 suggests that the excess mortality in older patients, many already infected with *P aeruginosa* before 1976, was related to inadequate anti-pseudomonas treatment. It is also probable that poor nutrition in older patients was the consequence of longstanding poorly controlled infection.

There is evidence that weight loss is caused by chronic lung infection.[5 27] Decreased protein synthesis and increased resting energy expenditure (REE) during acute exacerbations of chronic pulmonary disease have been reported in patients with cystic fibrosis[28] as well as a negative correlation between REE and pulmonary function.[29] Infection with *P aeruginosa* causes secretion of cytokines, including tumour necrosis factor alpha which acts as cachectin causing anorexia and weight loss.[30] In children with asthma the REE was significantly higher than in controls, probably as a result of the inflammatory process and the additional energy used in the work of breathing.[31] The strong correlation of BMI with dynamic lung function indices suggests that patients with poorer control of lower respiratory tract infections are those with the greatest loss of weight.

Normal growth in our patients with cystic fibrosis was thus achieved by an unrestricted diet and individual guidance on the addition of pancreatic enzymes, without the use of tube feeding or parenteral nutrition. However, decreasing weight and BMI occurred in patients over 15 years of age.

The issue of whether poor nutritional status is predominantly caused by longstanding infection or whether inadequate calorie intake leads to more aggressive lung disease is not solved in this study, but should be addressed in a prospective controlled clinical study.

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