Nutritional decline in cystic fibrosis related diabetes: The effect of intensive nutritional intervention

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Abstract

Background: Reports indicate that nutritional and respiratory decline occur up to four years prior to diagnosis of cystic fibrosis related diabetes (CFRD). Our aim was to establish whether intensive nutritional intervention prevents pre-diabetic nutritional decline in an adult population with CFRD.

Methods: 48 adult patients with CFRD were matched to 48 controls with CF, for age, gender and lung pathogen status. Nutritional and other clinical indices were recorded at annual intervals from six years before until two years after diagnosis. Data were also analysed to examine the impact of early and late acquisition of CFRD.

Results: No important differences in weight, height, body mass index (BMI), lung function or intravenous treatment were found between groups in the six years prior to diagnosis, nor any significant deviation over time. In those who developed diabetes, use of overnight enteral tube feeding (ETF) was four times as likely at the time of diagnosis, compared to controls [ETF 43.8% (CFRD) v 18.8% (CF Controls), OR 4.0, CI 1.3 to 16.4, p=0.01]. Age at onset of CFRD played a significant role in determining the pre-diabetic clinical course. Younger diabetics with continued growth (n=17) had a lower BMI from 2 years prior to diagnosis compared to controls [BMI 18.9 kg/m² (CFRD) v 20.8 kg/m² (CF Controls), diff=1.9, CI −0.1 to 3.7 p=0.04]. The BMI of older diabetics (completed growth at study onset) was equal to that of controls throughout.

Conclusion: Pre-diabetic nutritional decline is not inevitable in adults with CFRD, but is influenced by age of onset. In the group overall, those with CFRD are more likely to require ETF from 2 years prior to diagnosis. Despite intensive nutritional intervention, patients who continue to grow throughout the pre-diabetic years, show a level of nutritional decline absent in older adults.

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1. Introduction

Cystic fibrosis related diabetes (CFRD) is a well established complication of cystic fibrosis (CF). The condition is present in around 16% of the CF population, but is present in over 40% of those over thirty years of age [1,2]. Incidence is associated with increasing age, female gender and pancreatic insufficiency [3,4]. CFRD has been linked to a decline in lung function and nutritional status which occurs for several years prior to diagnosis of diabetes. Although insulin therapy leads to significant improvement in health status it does not fully reverse the negative impact on morbidity and mortality [4–8]. Deficits in nutritional status in patients with CFRD have been widely reported and are evident even in those patients who develop diabetes in their teenage years [4,6]. Surprisingly little is known about the potential impact of intensive early nutritional intervention in patients with CFRD. The major studies have focused on clinic

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populations where invasive enteral nutrition was absent or ill defined. Patients’ weight was often sub-optimal in the years preceding diagnosis of diabetes and at diagnosis itself, and may well have compounded a persistent nutritional deficit [5,6,9].

In contrast, data from the Leeds Adult CF Unit indicate no difference between the nutritional status of patients with and without CFRD [10], possibly due to our prolonged use of proactive nutritional interventions, including the use of high calorie oral nutritional supplements and enteral tube feeding and an established screening programme for diagnosis of CFRD.

Whilst we have shown that nutritional status can be maintained after diagnosis of CFRD, there is no evidence to suggest that the rate of nutritional and clinical decline can be modified prior to the onset of diabetes. The aim of this study was to establish whether intensive nutritional intervention can prevent nutritional decline prior to diagnosis of CFRD.

2. Methods

2.1. Subjects

All patients diagnosed with CFRD between 1995 and 2005 attending the regional adult cystic fibrosis unit, Leeds, UK, were included in this case control study. At the end of December 2005, 86 of 312 (28%) patients in total, were classified as diabetic within the clinic population. Forty eight patients fulfilled the inclusion criteria and were matched to a control with CF, without diabetes, nearest in age and of the same gender and lung pathogen status. The genetic mutation of each subject was noted as was the presence of meconium ileus at birth. Patients who were pancreatic sufficient, who had steroid induced CFRD, or gestational diabetes, and those who were diagnosed with CFRD after solid organ transplantation, were excluded.

2.2. Diagnosis of CFRD

Diagnosis of CFRD was based on the following criteria: a diabetic glucose tolerance test performed at a time of clinical stability, according to defined WHO criteria [11] followed by high pre- or post meal blood sugars requiring treatment with insulin; or acute presentation of high pre- or post-meal blood sugars requiring treatment with insulin.

Subjects followed our standard CF unit procedure for identification of CFRD. Patients undergo annual screening using the oral glucose tolerance test (OGTT) and undertake serial blood glucose monitoring where the result is classified within the diabetic or impaired range. The OGTT is repeated at 6 months where blood sugar monitoring does not indicate a requirement for insulin. Early re-assessment of glycaemic status is also considered between annual reviews according to UK consensus recommendations [12]. Pre and post-feed blood glucose monitoring is initiated when overnight enteral tube feeding is commenced.

2.3. Nutritional support

Nutritional support was initiated according to UK consensus guidelines [13] and was documented for each patient. Dietetic monitoring of patients occurred at each two-monthly out-patient appointment and at each consultation for intravenous antibiotic treatments. Where enteral tube feeding was initiated, this was infused overnight only and used as an adjunct to daytime oral nutritional intake.

2.4. Measurements

Data were collected annually from six years before diagnosis of CFRD to two years after diagnosis [weight (kg), height (m), BMI (kg/m²), forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC)]. These measures were the value at the point of diagnosis in the index case and the mean of values at out-patient attendance at the corresponding annual time points (+2 months). The number of days of intravenous antibiotic therapy was recorded as the mean number of days of treatment from six months before to six months after each time point. The prevalence of nutritional supplement intake and of enteral tube feeding was similarly calculated. Lung transplantation (after diagnosis of CFRD) and time of death was recorded.

Pulmonary function was assessed by means of standard spirometry using a Vitalograph Compact II Spirometer (Vitalograph Ltd, UK). The best measurement of three satisfactory efforts was documented. FEV₁ and FVC were compared with reference values and reported as the percentage of the predicted normal value.

2.5. Statistical analysis

Data that were normally distributed are set out as means plus or minus standard deviations Data were analysed using Stata 9 (StataCorp LP, Texas). Student’s paired t-tests and confidence intervals for paired means were used to compare differences between groups. ANOVA (repeated measures) was used to analyse trends over time. McNemar’s test and the paired method for calculating odds ratios were used to determine differences in oral supplement and enteral tube feed use. Alpha was set at 0.05.

Statistical power was calculated so as to detect a difference between groups of 1.0 in BMI at the time of diagnosis, using SD of pair wise difference as 3.28; at 80% power this estimate suggested a total sample size of 90 (45 cases and 45 controls).

The study was approved by the Leeds (East) Research Ethics Committee, Leeds Teaching Hospitals NHS Trust, UK.

3. Results

3.1. Patient demographics

Forty eight patients with CFRD and 48 controls were included in the study (Table 1). At the time of diagnosis of CFRD, 83% of participants had chronic Pseudomonas aeruginosa infection and 82% were homozygous for the p.Phe508del mutation. Similar proportions presented with meconium ileus at birth in the CFRD and control groups.
3.2. Nutritional indices

No significant differences were observed between patients with CFRD and controls for any nutritional parameter in the 6 years before the diagnosis of CFRD (Fig. 1). During this time period mean weight gain was 4.8 kg (CFRD) v 4.5 kg (CF Controls) and mean BMI increased from 19.5 kg/m² to 20.3 kg/m² (CFRD) v 20.0 kg/m² to 20.7 kg/m² (CF Controls). ANOVA (repeat measures) confirmed no differences between patients with CFRD and controls before the diagnosis of CFRD (F 6, 88)=7.9, p=0.38, and no deviation between patients with CFRD and controls over time, (F 6, 88)=0.2, p=0.98.

Two years after diagnosis, the mean BMI of patients with CFRD (21.5 kg/m²) had increased to a little above that of controls (20.6 kg/m²) [difference= 0.95, CI –1.1 to 1.2, p=0.9]. The heights of the two groups were almost identical at all time points [six years pre-diagnosis of CFRD,1.61 m v 1.62 m, at diagnosis 1.66 m v 1.66 m and two years post diagnosis 1.66 m v 1.66 m].

3.3. Oral nutritional supplements and enteral nutrition

Differences in oral nutritional supplement uptake were not significant at any point (Fig. 2). At six years before diagnosis oral nutritional supplement uptake was 24.4% (CFRD) v 16.3% (controls) [OR 2.3 CI 0.6 to 10, p=0.27], declining at the time of diagnosis of CFRD, just as uptake in CF controls reached its maximum (18.4% v 34.7%, OR 0.4, CI 0.1 to 1.2, p=0.09).

As diagnosis of CFRD approached, the proportion of patients receiving enteral tube feeding increased steadily (Fig. 2). The differences from controls became significant at one year before diagnosis (35.4% (CFRD) v 14.6% (CF Controls), OR 3.5, CI 1.1 to 14.6, p=0.03) and was greatest at the time of diagnosis (43.8% (CFRD) v 18.8% (CF Controls), OR 4.0, CI 1.3 to 16.4, p=0.01), when diagnosis of CFRD was shown to be four times as likely amongst patients who were prescribed overnight enteral tube feeding.

Nutritional supplements were in use at study onset (6 years pre-diagnosis), in order to maintain BMI within the normal range, [4(CFRD) v 4(CF Control)]; or to address a BMI <19 kg/m² [8(CFRD) v 2(CF Control)]. Enteral tube feeding was in place due to a previous fall in centile position [2 (CFRD) v 1 (Control); BMI <19 kg/m² and referred for transplant, [1(CFRD) v 0(Control)]; BMI <19 kg/m² [6(CFRD) v 3(Control)].

Of those who commenced enteral tube feeding throughout the study (11CFRD v 5 CF control), the presenting reasons were acute weight loss with BMI of <19 kg/m² in all cases, with the exception of 1 control who required enteral tube feeding to maintain a normal BMI for transplant. Mean % body weight loss in the year preceding enteral tube feeding was 8.5% (CFRD) v 2.9% (CF Control). Enteral tube feeding resulted in a mean weight gain of 7.0% body weight at 1 year and 9.9% at 2 years after start of enteral tube feeding in those with CFRD, compared to 2.5% and 7.2% in controls with CF.

![Fig. 1. Patients who develop CFRD compared to CF controls: nutritional status before and after diagnosis of diabetes.](image)
3.4. Pulmonary function

There was no significant difference in FEV₁ between patients with CFRD and controls at any time point [mean FEV₁ (six years pre) 61.2% v 67.5%, diff 6.3%, CI −3.4 to 16.1, \(p=0.2\), and (diagnosis) 46.2% v 53.7%, diff 7.5%, CI −1.1 to 16.1, \(p=0.08\)], nor were there any significant differences in FVC (Fig. 3). In diabetics a significant reduction in mean FEV₁ was observed from one year pre-diagnosis to the point of diagnosis [50.8% to 46.2%, diff=4.6% (CI 2.4 to 6.4, \(p<0.001\)], which stabilised on initiation of insulin therapy. There were no differences between CFRD v controls overall (\(F\) 1, 88)=0.8, \(p=0.38\), nor any deviation between the groups over time (\(F\) 6, 88)=0.2, \(p=0.98\).

3.5. Antibiotic treatment

Differences in the frequency of intravenous antibiotic treatment remained non-significant between groups at all time intervals [six years pre-diagnosis 14.7 v 15.7 days, CI −8.9 to 7.0, \(p=0.8\), yr 0 (diagnosis) 44 v 34.7 days, CI −6.1 to 24.6, \(p=0.23\). No significant deviation between CFRD and controls was observed pre diagnosis (\(F\) 6, 73)=1.4, \(p=0.22\).

3.6. Comparison of individuals with continued growth capacity versus those with completed growth

A sub-analysis was performed to determine whether the same nutritional and clinical course was followed for those who continued to grow in the six years before diagnosis (\(n=17\), age at diagnosis 21.9±3.7 years) and those whose growth was complete in the time period (\(n=31\), mean age 28.3±2.8 years).

In the younger patients in whom growth continued, differences in nutritional status emerged between patients with CFRD and their matched controls at two years pre-diagnosis [BMI 18.9 kg/m² (CFRD) v 20.8 kg/m² (CF Controls), diff=1.9, CI −0.1 to 3.7 \(p=0.04\)] and persisted until insulin therapy commenced (Fig. 4). BMI increased from 18.3 kg/m² to 19.6 kg/m².
one year after start of insulin therapy, returning this group to the same level as that of their non-diabetic controls. Those who developed CFRD were twice as likely to require oral nutritional supplements in the early pre-diabetic years (6 years pre-diagnosis) [47% v 17.6% OR 2.3 CI 0.6 to 10, \( p=0.54 \)], and were four times as likely to be enterally tube fed within the year of diagnosis (64.7% v 29.4% OR 4.0, CI 0.4 to 38.7, \( p=0.11 \)), although this did not reach significance. In this younger age group, \( \text{FEV}_1 \) remained 2–12% below that of controls throughout the study and declined significantly in the year prior to diagnosis, (46.9% to 41.5% diff= 5.4, CI 1.6 to 6.5, \( p=0.001 \)), stabilising on insulin therapy. Overall, there was no significant deviation in lung function between patients with CFRD and their controls, during the pre-diabetic phase (\( F_6, 21= 1.7, p=0.12 \)), nor were there any differences in level of antibiotic treatment.

In patients where growth was complete, there was no significant difference in mean BMI between patients with diabetes and their controls, throughout the pre-diabetic phase. No differences were seen in prevalence of oral sip feed use or enteral tube feeding; nor was there any significant reduction in lung function at any time point or any deviation in lung function over time (\( F_6, 47=0.28, p=0.9 \)).

4. Discussion

This case control study examines the impact of intensive nutritional intervention on the course of illness before diagnosis of CFRD. We have shown that nutritional decline is not an inevitable precursor to CFRD. Weight, height and BMI were similar to that of healthy controls throughout the pre-diabetic phase and did not decline prior to diagnosis. These findings differ from those of the previous published studies which demonstrate declining nutritional status prior to diagnosis of CFRD. Lanng et al. showed a progressive decline in nutritional indices from four years before diagnosis, while a study by Rolon et al. reported nutritional decline six months before diagnosis of diabetes in a younger population [5,9].

Both of these studies were comparable to our own in using a closely matched study design that accounted for age, gender and lung pathogen status. Subjects were pancreatic insufficient, with similar proportions of patients homozygous for p.Phe508del. There were, however, two important differences. Our population was significantly older and had better baseline nutritional status. More significantly, greater weight and BMI indices in our clinic population were associated with a high level of nutritional intervention. At the onset of our study around 40% of all patients were taking oral nutritional supplements and 25% were receiving enteral tube feeds, indicating an intense and pro-active nutritional approach that confirms previous reports from our clinic population [10].

Although there was a high overall prevalence of nutritional support, differences in the level of nutritional intervention emerged between those who developed diabetes and their controls. Difficulties in maintaining nutritional status in the early pre-diabetic phase resulted in a greater use of oral nutritional supplements in those with CFRD, whilst at the point of diagnosis of diabetes, patients were significantly more likely to be receiving overnight enteral tube feeding, when compared to their control population. This was sufficient to prevent nutritional decline throughout the pre-diabetic phase and emphasises the fact that more intensive nutritional intervention is required to maintain BMI in patients who develop CFRD. The effectiveness of enteral tube feeding was supported by the early reversal of nutritional deficits, equating to an increase in % body weight of around 7% and 10% at one and two years in those with CFRD.

Despite early differences in the level of nutritional support among the diabetic and non-diabetic groups, there was no evidence that lung function was significantly different or that greater levels of antibiotic treatment were required throughout the pre-diabetic period. This is in agreement with previous studies that have shown no significant difference in lung function leading up to diagnosis, but contrasts with their reports of insidious but significant deviation between groups over the same time period [5,9]. We hypothesise that maintaining nutritional
status throughout the pre-diabetic phase, may prevent the previously reported decline in lung function. Several studies have confirmed a strong relationship between lung function and nutritional status [14–16].

The greater intensity of nutritional support required to maintain nutritional status in the pre-diabetic group might suggest that nutritional intervention itself is a causative factor for diabetes. Millà et al. have shown that in a population with advanced lung disease (FEV1 < 40%), oral nutritional supplement intake can increase glucose excursion and insulin secretion [17]. They concluded that greater hyperglycaemia and higher glucose excursion after oral supplements were directly related to the carbohydrate content of oral supplements used, although no studies have directly related oral nutritional supplements to diabetes onset. The nature of the present study, precludes any causative relationship being shown, but requires further investigation.

A number of reports have proposed that CFRD is associated with enteral tube feeding; the incidence of diabetes ranging from 5%–50% within a one to two year follow-up period among tube-fed patients [18–21]. Enteral tube feeding prevalence at diagnosis of CFRD was 44% in our study which is consistent with previous research. Initiation of enteral tube feeding remains justified because of its effectiveness in producing weight gain in the short and longer term [18–21] and its impact on reducing malnutrition; itself an important independent predictor of mortality in CF [22].

Reversal of clinical and nutritional decline with insulin treatment is well documented [9,23,24], as are significant improvements in fat mass and percentage body fat at six months post-insulin therapy [25]. In line with these studies, and despite no significant deviation in nutritional wellbeing from controls, subtle sub-clinical deficiencies were present and were corrected with insulin therapy. We observed similar trends of 6% improvement in BMI and stabilisation in lung function after two years of insulin.

These improvements were especially striking in younger patients who had not completed their growth at the point of inclusion in the study. Their BMI remained 5–11% below that of their controls in the years preceding diagnosis but improved to around 1% with insulin therapy. These differences were not observed in an older group who had completed their growth by the time they were included in the study. Their nutritional status was the same as that of their control population throughout. Those who develop diabetes during adolescence and early adulthood appear to have a different pre-diabetic course.

This is not an unexpected finding. Younger subjects were approximately 16 years of age at entry; a period when growth and weight gain are continuing to increase. Pubertal growth spurts and the stress placed upon the body during this time might be expected to affect diabetics and controls equally before onset of diagnosis. We observed no differences in growth between CFRD and controls in this younger age group in the early pre-diabetic years, but did observe significantly poorer weight gain resulting in a lower BMI from two years before diagnosis. Younger diabetics are simply thinner and less well nourished than their controls from two years before diabetes onset. This is in agreement with epidemiological data which have shown that those who develop diabetes at an earlier stage (15–19 years) have greater nutritional compromise [6].

The effect of insulin therapy in improving these nutritional deficits was greater in younger adults than in the group as a whole. It suggests either that pre-diabetes in younger adults has a substantial impact that cannot be addressed through nutritional intervention, or that there is poor adherence to nutritional treatment or enzyme replacement therapy. Despite 65% of these patients receiving overnight enteral tube-feeding at the time of diagnosis, nutritional deficits remained. Nutritional compromise (BMI < 19 kg/m²) throughout the mid teenage years was evident in this group of patients.

Poorer nutritional status of younger adults in the pre-diabetic years may also reflect a greater level of impaired glucose tolerance in this age group. Our recording of overt diabetes alone in this current study, did not allow us to assess the presence of impaired glucose tolerance and its nutritional impact. Glucose tolerance abnormalities have been reported in 50% of patients with an unsatisfactory nutritional status as opposed to 15% in those who have not [26]. These differences suggest that abnormal glucose metabolism may have a considerable role in determining clinical course in this age group and requires more detailed assessment in our patients. Continuous subcutaneous blood glucose monitoring was not undertaken in this study, but is an important factor to consider in the future, particularly in younger adults with unexplained weight deficits.

In conclusion this study has shown that nutritional decline before the diagnosis of CFRD, is not inevitable, although adolescence is still associated with deteriorating nutritional status. Response to insulin treatment shows a powerful, insulin induced anabolic effect. Nutritional intervention is important in maintaining nutritional status in the population with CFRD overall, but cannot prevent weight loss in younger adults. Patients who develop CFRD are significantly more likely to receive overnight enteral tube feed within the year of diagnosis than controls, highlighting a potential causal relationship that requires further investigation. The impact of oral supplement and enteral feed composition, impaired glucose tolerance, adherence to treatment are all areas that may impact on diabetes outcome. Future work is needed to clarify their effect on nutritional status and in particular the impact of nutritional repletion on glucose metabolism and body composition in the pre-diabetic phase.

References


