Title: Nutritional outcomes in CF – are we doing enough?

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Summary

Although outcome data for individuals with cystic fibrosis (CF) have shown consistent improvements throughout the twentieth century, more recent national registry data suggests that outcomes have reached a plateau. Median values for nutritional outcomes in CF currently cluster around the fiftieth centile for the normal population. These data suggest that up to half of CF patients have sub-optimal body mass index (BMI) which might have a significant adverse impact on their respiratory status. BMI might be underestimating the extent to which more important lean body mass might also be reduced. Nutritional decline is a particular problem during adolescence and commonly persists into early adult life. Current treatment strategies to optimize nutrition include the use of high energy diets, proton pump inhibitors and optimal use of enzyme preparations including higher strength preparations to decrease pill burden. Whilst these are all of potential benefit, poor adherence to nutritional care recommendations is probably the greatest impediment to future health improvement. More effective strategies to impact on treatment adherence are needed.

Introduction

Maintaining good nutritional status is critical to the long-term survival of patients with Cystic Fibrosis (CF) and within the CF community much emphasis is placed upon the important association between poor nutrition and worsening lung function [1,2]. Analysis of outcome data obtained from the UK national registry of successive birth cohorts from the 1960s through to the 1990s showed progressive improvements in survival [3] and life table methods to predict survival of infants diagnosed at the beginning of the twenty-first century estimated that patients might expect to survive to a median age of over forty[4].

Port CF data

Port CF is the UK National database for CF patients. Outcome data from this registry for 2007- 2012 is shown in table 1. Although there might have been some incomplete data collection in the earlier years, these data suggest that more recently there has been very little improvement in clinically relevant outcome parameters pertaining to nutrition and respiratory status. New treatments such as Ivacaftor (Kalydeko), a CF potentiator, have been of considerable clinical benefit, but only approximately 5% of the UK CF population are suitable and it has only been widely available since 2012. Advances in CF care in the 6 years before this drug's release, have largely been confined to improved service delivery of existing treatments. Such developments appear to have had little impact on the outcome measures shown, and suggest a need for a change of emphasis in clinical care.

The median BMI in the UK is 22 for adults and just above the 50th centile for children. Whilst it might seem encouraging to observe that the overall body mass index (BMI) distribution of the CF population approximates to that of the normal UK population, this belies the fact that the median BMI decreases during late childhood and persists at a lower level into early adult life. This is a critical time for patients and the decline thus far has been poorly responsive to recent increases in specialist services and the provision of good transition from paediatric to adult care.

BMI, lean body mass and Lung function

There is a clear association between reduction in BMI to below the 50th centile and reduced lung function expressed as FEV1% predicted. This relationship persists in analyses restricted to pancreatic insufficient patients who are homozygous for the DeltaF508 genotype, and a linear positive relationship between BMI and lung function continues above the 50th centile, albeit at a less steep incline [5]. A longitudinal cohort study from Toronto confirms this relationship between improved lung function amongst individuals who might be considered to be overweight or even obese, but points out that the benefits of a BMI above 25kg/m2 are small and need to be balanced against the known long term health risks associated with obesity [6].

Many previous reviews have stressed the importance of aggressive nutritional support, encouraging a high calorie, high protein, unrestricted diet to promote normal growth [7]. The US cystic fibrosis foundation recommends that all CF children should have a BMI above the 50th centile and all CF adults a BMI > 22 [8]. Current UK outcome data would suggest that these nutritional outcomes are not being achieved in almost a half of the UK CF population.

Even if a BMI above the 50th centile is achieved for all patients, this might not be enough to ensure that nutritional factors are not still adversely impacting on respiratory outcomes. A recent cross sectional study of nutritional parameters from the Children's hospital of Philadelphia, has helped clarify the important relationship between BMI and lean body mass (LBM) in CF [9]. Using spine and whole body dual energy X-ray absorptiometry, the group were able to estimate LBM and fat mass in their CF patients in comparison to a healthy

control population. These data were used to determine the extent to which BMI is a proxy indicator of lean body mass, the latter being a more important determinant of respiratory muscle strength, lung function and overall physical well being. Although BMI was shown to be a relatively useful indicator of nutritional status, the study highlighted important sex differences in body composition in the CF population compared to normal controls. In particular data showed that a low lean body mass index (LBMI) was associated with worse lung function in males irrespective of whether their BMI was above or below the 50th centile. In females, a lower LBMI was only associated with worse lung function if their BMI was sub-optimal. Studies such as this suggest the potential value of measurements of LBM as a part of routine clinical care, and in particular to detect a reduced LBMI in boys who are achieving their target BMI. These data also highlight the need for longitudinal studies to define the interventions that are likely to be effective, not just to improve BMI to above the 50th centile, but also to achieve improvements in LBMI, irrespective of BMI, to maximise overall health.

This issue is complex, and the relationship between LBM, fat mass and optimal strategies to improve nutrition to stabilise lung function are unclear. This has been highlighted in a recent adult study where enteral feeds were reported as stabilising lung function as result of increased android fat distribution, a known risk factor for diabetes, but with little impact on lean body mass [10].

BMI, lean body mass and resting energy expenditure

Although port CF data suggests that a decline in BMI tends to predate reduced lung function, there is a clearly a complex relationship between nutritional intake, lung infection, and metabolic demand. A study of the effect of chronic infection with pseudomonas on resting

energy expenditure, (REE) expressed as kilo calories per unit of lean body mass, demonstrated a 50% increase in REE compared to individuals without chronic infection [11]. These findings highlight how the inflammatory burden, and increased work of breathing associated with pulmonary sepsis, contributes to a vicious cycle of decreasing muscle mass and worsening respiratory status.

Proton pump inhibitors

Medical interventions to improve nutritional status are largely limited to adjustments of either pancreatic enzyme dose or formulation, and the use of acid suppression treatment. The use of proton pump inhibitors (PPIs) to raise proximal small bowel pH, and thus optimise enzyme efficacy, has increased significantly over recent years. In 2012, 40.5% of the UK CF population were prescribed PPIs (table 2). Whilst there is limited evidence that PPIs reduce gastric acidity and improve fat absorption, published studies thus far have not determined whether their long term use improves nutritional status and/or lung function [12]. This class of drugs has the potential for side effects that are worthy of consideration. Studies of the use of PPIs in non CF patient groups have shown a dose related risk for community acquired pneumonia after short term use [13], and a recent study in CF has raised the possibility of an association between the use of esomeprazole and risk of pulmonary exacerbation [14]. Other observations that might be of relevance to CF patients is the association between prolonged PPI use and increased relative risk of fractures as demonstrated in a UK wide primary care based study and corroborated by a large meta-analysis [15, 16].

Pancreatic enzymes

Eighty-four per cent of the UK CF population are pancreatic insufficient, and the median recorded daily lipase dose has remained much the same between 2007-2012 (Table 2). Lipase doses are higher amongst those taking higher strength preparations (Figure 1), although in a post marketing survey following the introduction of Creon 40,000, the mean daily lipase dose was decreased by an average of 11% compared to the doses used at baseline [17].

A recent US study comparing outcomes between different centres, showed a significant difference in median enzyme dose between centres in the highest and lowest quartile groups for BMI centile [18]. Whilst these findings suggest that using higher enzyme doses might improve CF outcomes, the range of doses reported were relatively low compared to those used in the UK, and the difference in doses between the centres with the best and the worse outcomes were relatively small. Historical concerns about the risks of fibrosing colonopathy in relation to excessive enzyme usage are noteworthy, but it would appear that current UK practice for enzyme use is not associated with the occurrence of this complication [19] (figure 1).

Non-adherence

Pill burden, in relation to the number of capsules that have to be ingested, rather than absolute dose of pancreatic enzyme, is potentially of greater relevance to the optimal correction of malabsorption in clinical practice. Studies in patients with HIV of treatment related determinants of non adherence identified that a high pill burden, of more than 10 pills per day, was more predictive of non adherence to anti-retroviral therapy than other risk factors

including the occurrence of side effects, anxiety, depression, alcohol and substance abuse and dosing regimen [20]. A review of studies addressing non-adherence in cystic fibrosis has recently been reported [21]. Whilst the researchers noted there were significant limitations in our current understanding of the prevalence of non-adherence in CF, the limited data available suggested that the lowest levels of adherence were to nutritional aspects of care. Such findings emphasize how strategies to address non-adherence are of central importance in enabling CF patients to gain optimal benefit from currently available therapies. Addressing these unmet needs, with a particular focus on the nutritional requirements of patients below the 50th centile for BMI in the first instance, would seem a worthwhile approach towards achieving future improvements in clinically relevant outcomes.

Table 1. CF Registry data 2007-2012

	Year					
	2007	2008	2009	2010	2011	2012
Number of reports	4408	6082	7377	7937	8679	8795
Male n (%)	2375 (53.9)	3239 (53.3)	3916 (53.1)	4217 (53.1)	4621 (53.2)	4621 (52.5)
Age	18.3 (10.0, 26.7)	18.1 (9.8, 26.6)	17.8 (9.4, 26.9)	17.9 (9.3, 27.8)	18.3 (9.3, 27.8)	18.6 (9.3, 28.2)
FEV_1 (% of predicted)	72.6 (24.8)	72.0 (24.6)	71.8 (24.4)	71.6 (24.4)	72.4 (24.5)	71.7 (24.7)
BMI						
Adult (kg/m^2)	21.7 (16.8, 23.9)	21.7 (19.7, 24.0)	21.7 (19.8, 24)	21.4 (19.5, 23.6)	22.0 (20.0, 24.4)	22.0 (20.0, 24.4)
Child ≤ 17 years centile	53.3 (26.9, 75.4)	51.7 (26.6, 74.3)	51.1 (25.9, 75.5)	52.2 (28.5, 75.0)	53.8 (28.0, 76.7)	52.7 (28.1, 75.5)

All continuous data except FEV_1 were skewed so are expressed as medians (interquartile ranges). FEV_1 was approximately normally distributed and is expressed as mean, (standard deviation).

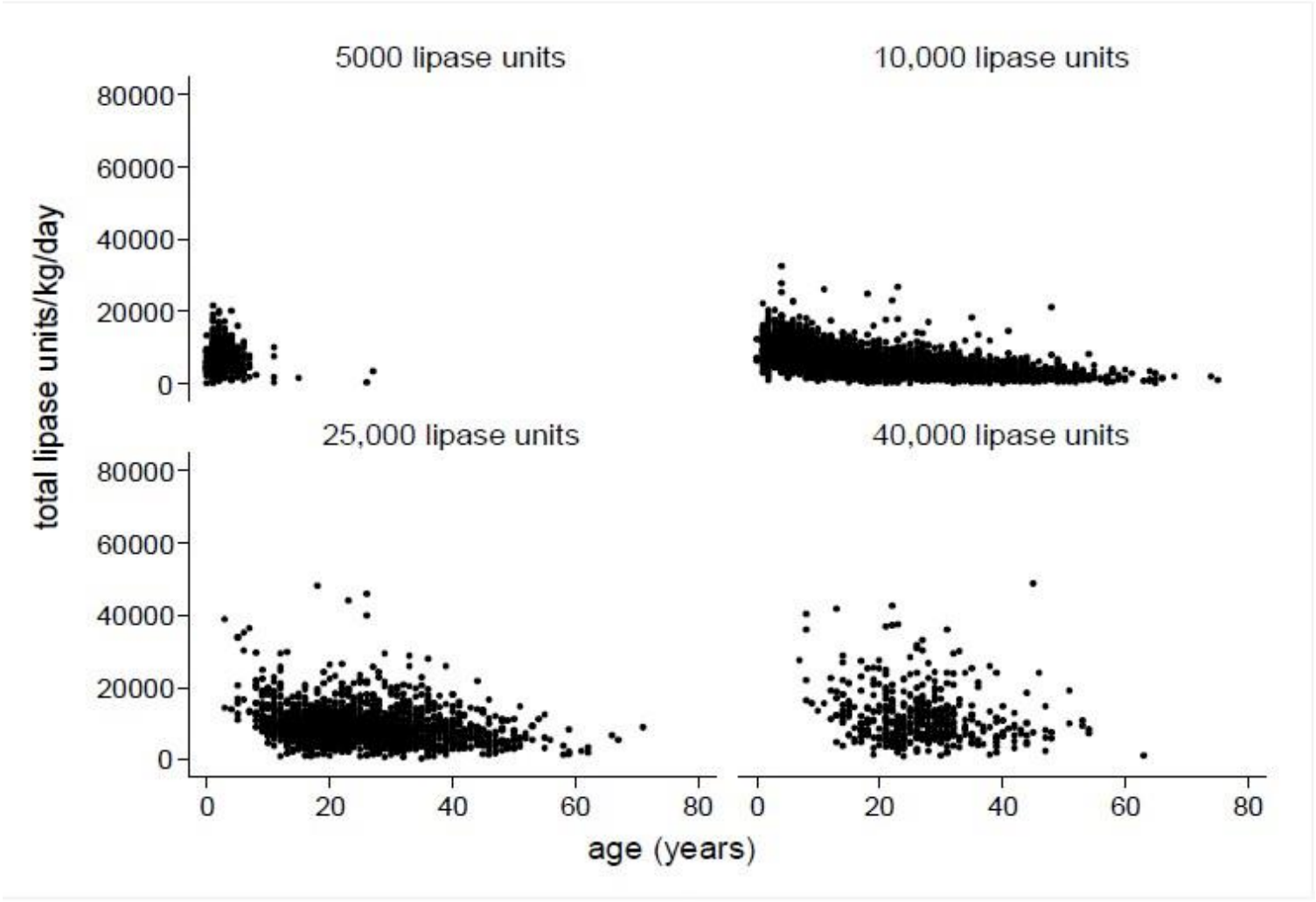
Table 2. Pancreatin and acid suppression therapy

	Year					
	2007	2008	2009	2010	2011	2012
Proton pump inhibitor n (%)	970 (22.0)	1653 (27.2)	2267 (30.7)	2776 (35.0)	3326 (38.3)	3560 (40.5)
H2 antagonist n (%)	169 (3.8)	261 (4.3)	331 (4.5)	360 (4.5)	448 (5.2)	474 (5.4)
Antacid n (%)	26 (0.6)	72 (1.2)	74 (1.0)	100 (1.3)	102 (1.2)	130 (1.5)
Pancreatic enzymes n (%)	3145 (71.3)	4835 (79.5)	5975 (81.0)	6672 (84.1)	7328 (84.4)	7389 (84.0)
≥10,000 units lipase/kg/day n (%)	626 (20.8)	973 (21.1)	1239 (21.9)	1507 (23.3)	1559 (22.3)	1464 (21.2)
Total lipase/kg/day median (IQR)	6632 (4184, 9404)	6832 (4314, 9469)	7026 (4474, 9615)	7022 (4521, 9746)	6937 (4395, 9615)	6842 (4371, 9459)

Percentages are percentage of all patients contributing data except lipase dose where those not on lipase replacement therapy are excluded from analysis. Lipase dose data are skewed so are expressed as medians (interquartile ranges).

Figure 1. Relationship between pancreatic enzyme dose (lipase units/kg/day) and age enzyme preparation (2012 data, n=7,164)*

Footer: * data not shown for 175 patients (2.0%) taking multiple preparations and 50 patients (0.6%) taking alternative enzyme preparations not displayed above.


5000 lipase units
10,000 lipase units
25,000 lipase units
40,000 lipase units
total lipase units/kg/day
80000
60000
40000
20000
0
0
20
40
60
80
age (years)

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Declaration of interest

Dr Connett has been a member of advisory boards and an invited speaker at meetings sponsored by Novartis, Forest and Abbott.

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