囊性纖維變性疾病中體細胞質量和蛋白質能量代謝的改變

The body cell mass and altered protein energy metabolism in cystic fibrosis

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To further investigate the body cell mass (BCM) in CF, as the central metabolically active body compartment, and to determine if measures used as reference standards after comparative differences in protein energy metabolism, BCM was measured by K^{40} analysis (n=144 CF, 69 M, 71F, ages 0.3-17 years) related to age and gender control date (n=1478). Protein synthesis was studied by whole body C^{13} leucine kinetics (LSYN, n=10 well nourished vs 7 undernourished CFs matched for Ht, Sex and FEV_1). Energy expenditure (REE) was studied by indirect calorimetry (n=4 ΔF508 CF infants with no lung disease vs n=12 age, wt, ht and sex matched healthy infants). BCM was <1 sd below 50th centile in 75% of CFs although only 15 and 10% had weights or heights <1 sd below 50th centile. Mean LSYN and REE did not significantly differ between groups in absolute values or corrected for weight, height or surface area, but were accelerated (P<0/01) when corrected for BCM.

The adverse effects of malnutrition on morbidity and mortality in cystic fibrosis (CF) and the importance of therapy to prevent or treat nutritional deficits in this disease are well documented[1,2]. There are multiple inter-related factors which affect the nutritional status of patients with this disorder, many of which are not yet fully understood. It seems likely that an inadequate nutrient intake combined with nutrient losses from malabsorption are important in the pathogenesis, but the role of alterations in energy expenditure and protein turnover have not been fully explored.

Results indicating increased energy expenditure[3,4] and discordant results indicating normal or accelerated protein turnover[5,6] have not, to date, taken into account the differences that exist in body compartments, specifically body cell mass (BCM) – the central metabolically active body compartment – between well-nourished and malnourished groups. Random measurements of body weight and fat-free body mass are inaccurate markers of BCM and do not take into account processes that alter body composition (especially the relationship between extracellular and intracellular water), hence the need for direct measurement of BCM[7,8] as a meaningful reference standard when comparing differences in physiological processes such as protein turnover and energy expenditure. This may be particularly pertinent in CF where we have shown significant deficits in the growth of BCM, as measured by total body potassium[9].

As the body protein reserve plays an important role in energy provision in malnutrition, knowledge of the extent of body stores and turnover would be of considerable value in accurately defining the nutritional deficit in this disease.

This study was undertaken to determine if measures used as reference standards alter comparative differences in protein energy metabolism, and to further investigate the role of the BCM in CF.

Methods

Protein synthesis and flux was studied by C^{13} leucine kinetics (LSYN) in ten well-nourished and seven undernourished CF patients matched for height, sex and FEV1. All were selected in the prepubertal age group because of relative uniformity of normal body composition with minimal sex differences, and all were in a stable clinical condition. The use of the leucine model, its assumptions and validation have been described in detail elsewhere[10]. 'Undernourished' was defined as a decline in wt Z score of >1.0 over the previous 12 months or a wt X score of <1.0. None had hypoproteineaemia or biochemical/clinical evidence of liver disease.

Resting energy expenditure (REE) was studied by open circuit indirect calorimetry in six homozygous δf508 CF infants with no clinical evidence of lung disease and 39 age, wt, ht and sex-matched control infants.

Body cell mass was measured by total body potassium determination in 144 CF patients (69m, 0.3-17years) including those who had had LSYN and REE measured as above related to age and sex controldata (n=1478). This measures the intensity of the 1.46 MeV γ ray emitted by K^{40} using a shadow shield type whole body counter (Assuscan, Canberra Industries, Boston, MA, USA) previously calibrated for use in infants and children at the Royal Children's Hospital, Brisbane[9]. The coefficient of variation of a 40-minute study of a 30 kg child (potassium content 60g) is ±4%. BCM was calculated assuming that K is distributed 98% within the BCM and that this is independent of the CF disease process, as has been shown previously[11].

Statistical analysis was by Student t-test and all data were expressed as mean ±SD.

Results

Mean LSYN did not significantly differ between groups in absolute values or corrected for wt, ht or surface area, but was accelerated when corrected for BCM ($P<0.001$), (Table 1). There was a greater increase of REE in the CF group over controls when compared in terms of BCM (115%) than if expressed in units of wt, ht or surface area (111%), (Table 2). BCM was >1 SD below the 50th centile in 75% of CFs although only 15% and 10% had wt or ht <1 SD below the 50th centile.

Table 1. Mean study results: LSYN corrected for wt, ht, surface area and BCM.

Leucine synthesis (g)	CF mal (n=7)	CF well (n=10)	Compar (diff)	P
/Wt (/kg/d)	4.5 (1.2)	3.8 (1.2)	115%	ns
/Ht (/cm/d)	0.98 (0.2)	0.82 (0.27)	119%	ns
/BSA (/m^2d)	125 (29)	105 (32)	119%	ns
/BCM (/g of K/d)	2.5 (0.6)	1.4 (0.4)	147%	<0.001

Table 2. Mean study results (CF, controls) for REE.

Resting energy expenditure (MJ)	CFδF508 (n=6)	Control (n=39)	Compar (diff)	P
/wt(/kg/d)	0.238 (0.025)	0.213 (0.025)	111%	<0.05
/ht(/cm/d)	0.0244 (0.0054)	0.022 (0.005)	111%	<0.005
/BSA(/m^2/d)	4.56 (0.7)	4.08 (0.57)	111%	ns
/BCM(/g of K/d)	0.163 (0.021)	0.142 (0.027)	115%	<0.02

Discussion

These studies emphasise the importance of determining specific body composition measurements when investigating physiological processes in disease sites, and of using appropriate reference standards (ie, BCM) when comparing protein energy metabolism in different groups. C^{13} leucine turnover was significantly accelerated in the malnourished group when analysed in terms of BCM, but not with reference to absolute values or for wt, ht or BSA, suggesting that significant depletion of BCM is characterized also by significant increases in protein turnover. CF is characterized by a protein energy deficit resembling that of protein energy malnutrition but *in contrast* to the normal adaptive response, protein turnover in CF is markedly increased.

Resting energy expenditure (REE) was found to be increased to a significant degree in CF patients compared with controls only when expressed in terms of BCM. Moore has argued against the concept of using lean body mass because this is a heterogenous compartment containing both fast-metabolizing energy using components such as plasma proteins, as well as slow metabolizing components such as collagen[8].

This observed increase of REE/unit BCM in CF may be due to an energy-requiring effect of the basic defect and/or clinically undetectable lung pathology and further studies including objective infant lung function studies and bronchoscopies are being carried out in order to clarify this point.

In conclusion there is further evidence for the maladaptive increase in protein turnover in response to protein energy deficit of CF patients, but more importantly it must be emphasised that deficits in BCM are common in CF and the alteration in body compartment distribution contributes to the apparently poor sensitivity of normal reference standards in the assessment of clinically important inadequate nutritional state.

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