Whole body protein turnover in childhood Crohn's disease

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Abstract

In order to investigate the effects of treatment on protein metabolism in childhood Crohn's disease whole body protein turnover was measured using a primed constant intravenous infusion of L-[1-¹³C]leucine and mass spectrometry in 10 children with active disease. Mean rates of protein synthesis and breakdown markedly decreased after treatment with steroids (four) or an elemental diet (six). This suggests that protein synthesis and breakdown are increased during active Crohn's disease in children and are reduced after induction of remission regardless of the type of treatment.

There are conflicting views on protein metabolism in chronic inflammatory bowel disease. Using a stable isotope amino acid tracer, L-[1-¹³C]leucine, Motil *et al*¹ showed similar rates of whole body protein turnover – that is, synthesis and breakdown – in six adolescents with active Crohn's disease and five healthy controls. Chronic inflammation and steroid therapy, surprisingly, had no apparent effect on protein turnover. Powell-Tuck and colleagues,² however, showed that protein turnover increased with disease activity in 19 adults with inflammatory bowel disease. The aims of this study were therefore: (i) To determine whether whole body protein turnover is related to disease activity in childhood Crohn's disease. (ii) To determine possible effects of treatment with steroids and an elemental diet on whole body protein turnover.

Methods

PATIENTS

Ten children with active Crohn's disease were studied, all had normal growth. Their ages, site and duration of disease activity are indicated in Table I. The diagnosis was confirmed by clinical, radiological, and histological features. Disease activity was indicated by: increased stool frequency, abdominal pain, weight loss, raised serum orosomucoid, raised erythrocyte sedimentation rate, reduced serum albumin. Activity was graded according to the Lloyd-Still activity index.³ Dietary intake was assessed by five day weighed surveys. On diagnosis of relapse the patients were randomly allocated to one of two treatment groups: group A (four patients) received prednisolone (2 mg/kg/day, maximum 60 mg/day) and sulphasalazine (25 mg/kg/day), they continued to eat a normal diet. The dosage of prednisolone was reduced after two weeks according to clinical response; group B (six patients) received an elemental diet orally

(Elemental 028; amino acids 12%, carbohydrate 77.8%, fat 6.64%, energy 399 kcal/100 g before reconstitution with water) (Scientific Hospital Supplies, Liverpool). Energy intake was adjusted to the recommended daily allowance.⁴ No other food or drink was allowed for four to six weeks then normal foods were gradually reintroduced depending on clinical response.

All patients were studied before and after four weeks treatment, when back in remission.

EXPERIMENTAL DESIGN

Whole body protein turnover was determined by the leucine kinetic model.⁵ After an overnight fast, infusion and venous blood sampling lines were set up in contralateral forearm veins before commencing the infusion. At time 0, priming doses of L-[1-¹³C]leucine (0.66 mg/kg) and NaH¹³CO₃ (0.08 mg/kg) were given, then a constant infusion of L-[1-¹³C]leucine (0.5 mg/kg/h) was started and continued for 150 minutes. Total CO₂ production rate was measured (Beckmann metabolic chart) before the infusion, after 90 and 150 minutes. Expired breath samples for ¹³CO₂ were collected into vacutainers (ref 606433, Becton Dickinson, Rutherford, New Jersey, USA) before the infusion and each 15 minutes after it was calculated that plasma leucine would have reached plateau levels.

Venous blood samples were collected at the same times as breath samples and the plasma immediately separated and frozen. L-[1-¹³C] ketoisocaproic acid enrichment was determined as described previously.⁶ Whole body leucine flux was calculated from the rate of administration of L-[1-¹³C]leucine and the extent of labeling of plasma L-[1-¹³C]ketoisocaproic acid as this is thought to be a better indicator of intracellular leucine metabolism than plasma leucine.⁶ The rate of leucine oxidation to CO₂ was calculated from the total CO₂ production rate and the breath ¹³CO₂ concentration.

STATISTICAL ANALYSIS

Results are expressed in terms of the mean and 95% confidence interval. The paired *t* test was used to compare disease activity, energy intake, and rates of protein turnover before and after treatment.

Results

WHOLE BODY PROTEIN TURNOVER

Plateau enrichments of breath ¹³CO₂, and plasma L-[1-¹³C]ketoisocaproic acid were achieved during the last 60 minutes. Rates of protein breakdown invariably exceeded rates of

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TABLE I Characteristics of the patients

Patient number	Age (yr)	Duration (yr)	Sites	Treatment Group
1	13.9	2.1	Colon	Steroids
2	17.5	2.0	Ileum+colon	
3	15.5	0.4	Ileum+colon	
4	8.3	0.2	Colon	
Mean	13.8	1.2		
5	17.0	3.2	Ileum+colon	Elemental diet
6	11.5	1.0	Ileum	
7	11.9	2.4	Ileum	
8	12.9	0.6	Colon	
9	14.4	1.1	Ileum	
10	8.2	0.1	Colon	
Mean	13.1	1.4		

synthesis, as expected for studies carried out in the postabsorptive state. Mean rates of whole body protein synthesis and breakdown decreased markedly in both treatment groups (Table II) but there were no significant changes in protein balance (synthesis-breakdown) before and after treatment.

ENERGY INTAKE

The mean energy intake increased from 85% to 130% of the recommended daily allowance in the steroid treated group and from 87% to 112% in the elemental diet treated group (Table III).

DISEASE ACTIVITY

The mean increase in the Lloyd-Still activity index was 13 (74 to 87) in the group treated with the elemental diet, not significantly different from the mean increase of 14 (70 to 84) in the group treated with steroids. In the patients with predominantly colonic disease (two treated with steroids and two treated with elemental diet) the mean increase in activity index was 9.5 in each of the two treatment groups (Table III).

Discussion

These results confirm an earlier study that elemental diets are as effective as steroids in the treatment of acute childhood Crohn's disease.⁷ Some authors have described a poorer therapeutic response in patients with predominantly colonic involvement⁸ but others have found that elemental diets may be effective in such patients.^{9,10} In the present study, the elemental diet was as effective as steroids in the treatment of predominantly colonic disease but there were only two patients in each treatment group. A recent randomised study has suggested that the time to relapse may be shorter in children treated

TABLE III Energy intake and disease activity pre and post treatment

Patient number	Activity index		Energy intake (%RDA)		Treatment group
	Pre	Post	Pre	Post	
1	87	93	68	94	Steroids
2	64	85	72	94	
3	74	88	116	151	
4	53	69	85	181	
Mean	70	84	85	130	
p	0.02		0.08		
5	67	74	32	106	Elemental diet
6	80	89	101	152	
7	68	93	88	91	
8	84	90	98	106	
9	72	91	98	106	
10	74	87	102	112	
Mean	74	87	86	112	
p	0.008		0.08		
All patients					
Mean	72	86	86	119	
p	<0.001		0.008		

RDA=recommended daily allowance.

with an elemental diet than in those treated with steroids¹¹ but a retrospective study in adults showed no significant difference in longterm relapse rates.¹⁰

The marked decrease in rates of whole body protein turnover in both treatment groups supports the findings of Powell-Tuck *et al.*² that protein turnover is correlated with disease activity and contrasts with the results of Motil *et al.*¹ that acute inflammation and steroid therapy had no effect on whole body protein turnover. The reason for the discrepancy is uncertain but may be related to differences in the patient study groups. Motil's patients all had growth failure, a protein intake exceeding the recommended daily allowance and an energy intake appropriate for the height age. They were studied in the fed state and four patients were on steroids at the time of the study. The patients in the present study were initially on no treatment and had normal growth, suggesting milder disease activity. Energy intake was well below the recommended daily allowance initially but increased substantially after starting treatment.

The patients were all in negative protein balance and despite the changes in protein turnover there were no significant differences in overall protein balance before and after treatment. This presumably reflects the fact that the studies were carried out in the postabsorptive state and further studies are required in fed patients. All of the children in this study had normal growth and further studies are also required to examine the relationship between protein turnover, growth failure, and the effects of therapeutic intervention. The elemental diet was well tolerated orally and may be considered as the treatment of choice, thus avoiding the side effects associated with steroid therapy.

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TABLE II Whole body protein turnover in childhood Crohn's disease (mean and 95% confidence interval)

	All patients	Elemental diet	Steroids
n	10	6	4
Protein pretreatment	152 (131 to 172)	152 (123 to 181)	151 (95 to 206)
Synthesis post treatment	121 (107 to 135)	124 (104 to 143)	117 (79 to 155)
p	0.001	0.031	0.036
Protein pretreatment	170 (146 to 194)	167 (133 to 201)	174 (112 to 236)
Breakdown post treatment	138 (121 to 154)	136 (116 to 156)	140 (91 to 189)
p	0.002	0.041	0.043
Protein pretreatment	-18.3 (-12.0 to -24.6)	-14.8 (-7.4 to -22.3)	-23.5 (-8.8 to -38.2)
Balance post treatment	-16.4 (-9.1 to -23.7)	-12.2 (-6.2 to -18.2)	-22.8 (-2.0 to -43.5)
p	0.551	0.369	0.923

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