Plasma polyunsaturated fatty acid pattern in active inflammatory bowel disease

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Abstract

Plasma fatty acid patterns were assessed by gas liquid chromatography in 73 patients with active inflammatory bowel disease and 107 healthy controls. The influence of the disease activity on fatty acid profile was also investigated. Plasma fatty acid patterns in patients with ulcerative colitis and Crohn's disease were similar. Plasma C18:3n3 and C22:6n3 were significantly higher in active ulcerative colitis ($p=0.0143$ and $p<0.00001$ respectively) and in Crohn's disease ($p<0.00001$ for both) than in controls, whereas C20:3n6 was significantly lower in patients than in controls, both in ulcerative colitis ($p=0.0001$) and in Crohn's disease ($p=0.0041$). In more severe disease, plasma polyunsaturated fatty acid concentrations fell with a significant stepwise decrease in the desaturation index ($p=0.0031$ in ulcerative colitis and $p=0.0355$ in Crohn's disease). Even in patients with severe disease, however, plasma n3 fatty acids (C18:3n3 and C22:6n3) never fell below those of healthy controls. These findings suggest that in active inflammatory bowel disease, an increased biosynthesis might coexist with an increased consumption of polyunsaturated fatty acids. These observations may be of relevance in the pathogenesis of the disease as polyunsaturated fatty acids are involved in tissue eicosanoid synthesis and cellular membrane function, including that of immunocompetent cells. These results also question the rationale of using n3 polyunsaturated fatty acids in the treatment of inflammatory bowel disease.

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Polyunsaturated fatty acids have essential biological functions. As part of the structure of cell membrane, they exert control on its intrinsic proteins – for example, enzymes, receptors – by inducing changes in membrane fluidity.[1,2] In addition, the long chain polyunsaturated fatty acids, dihomo-γ-linolenic (C20:3n6),[3] arachidonic (C20:4n6),[4,5] and eicosapentaenoic (C20:5n3)[6] acids are the precursors of eicosanoids. Some of the arachidonic acid derived eicosanoids (prostaglandin E_2, leukotriene B_4, and thromboxane A_2) have been incriminated in the pathogenesis of inflammatory bowel disease, because their concentrations increase in the inflamed intestinal mucosa in the acute phase of the disease.[7–12]

There are four different polyunsaturated fatty acid series which share the same desaturases and elongases for their synthesis.[13,14] Their affinity for these enzymatic systems are different, however. In addition, the components of the different fatty acid series are not interconvertible in vivo.[13] These properties have allowed modification of the eicosanoid synthesis by producing changes in dietary polyunsaturated fatty acids.[15,16] Dietary supplementation with eicosapentaenoic and docosahexaenoic acids rich fish oil induces the appearance of triene prostaglandins and thromboxanes[17,18] and pentaene leukotrienes[19] with attenuated inflammatory effects.[17–19] The therapeutic efficiency of eicosapentaenoic acid (C20:5n3) as an antiinflammatory agent in experimental models of inflammation[20,21] and therapeutic trials in patients with rheumatoid arthritis[22] and inflammatory bowel disease[23–25] is, however, at least, controversial.

Plasma polyunsaturated fatty acid patterns have not been previously assessed in ulcerative colitis whereas information in Crohn's disease is limited.[26,27] It would be of scientific interest to know of plasma polyunsaturated fatty acids profile in inflammatory bowel disease as it might have both pathophysiological and therapeutic implications.

The aim of this study was to prospectively assess the plasma fatty acid pattern in patients with active inflammatory bowel disease compared with healthy controls and to ascertain whether the activity of the disease has any influence upon plasma concentrations of fatty acids.

Methods

PATIENTS

Seventy three consecutive patients (40 men, 33 women) with active inflammatory bowel disease (median age 32·5 years; ranges 14–81) were included in the study at admission or when first seen in the outpatient clinic. Forty one had ulcerative colitis and 32 had Crohn's disease. The diagnosis of inflammatory bowel disease was based upon clinical, endoscopic and radiological findings and was supported by biochemical, scintigraphic and pathological features. Exhaustive microbiological analysis were performed in order to exclude patients with gastrointestinal infection. These included in all cases stool culture, special stool culture and serologic tests for *Yersinia enterocolitica*, repeated fresh stool examination (three to six) for parasites and chlamydia direct immunofluorescent test. *Clostridium difficile* toxin assays, biopsy examination and culture for mycobacteria and immunohistochemical detection of herpes virus and cytomegalovirus in biopsy specimens were carried out in particular cases.

The activity of the disease was assessed by

means of the Truelove's index for ulcerative colitis[28] and the Van Hees's index for Crohn's disease.[29] According to the activity index, the attack was classified as mild, moderate, or severe. Twelve patients with ulcerative colitis had mild, 19 moderate, and 10 severe attacks. In Crohn's disease, the activity was mild in 15, moderate in 11, and severe in six patients. Data regarding diet, nutritional status,[30] and drugs were also carefully recorded.

CONTROLS

One hundred and seven healthy individuals (46 men, 61 women; median age 32·5 years; ranges 18–76) living in an urban area in the outskirts of Barcelona (Catalunya, Spain) acted as a control group. All subjects were well nourished according to previously described criteria.[30] The existence of both acute and chronic illnesses was ruled out on the basis of a complete anamnesis and full clinical and biological examination including routine haematological counts, serum glycaemia, total cholesterol, triglycerides, and renal and liver function tests (Technicon SMA-20 Autoanalyzer). Those with previous history of diseases or surgical procedures capable of influencing the absorption of macro or micronutrients were also excluded from the study. All subjects, including elderly people, lived at their family home and were on a balanced western diet. Intake of monotonous, deficient, vegetarian or lacto ovo vegetarian diets was ruled out. Alcohol intake was lower than 40 g/day for men and 20 g/day for women. Habitual drug intake in the previous three months of sample extraction was carefully ruled out, especially for hypolipemiant drugs, non-steroidal antiinflammatory drugs or oral contraceptives. Individuals taking trace elements or vitamin supplements in the previous six months were not included. Relatives of patients with inflammatory bowel disease were also excluded.

Informed consent was obtained from each patient. The study was performed in accordance with the 1975 Declaration of Helsinki ethical guidelines and was approved by the Research and Ethical Committees of the Hospital.

TABLE I *Clinical features of the patients*

	Ulcerative colitis (n=41)	*Crohn's disease (n=32)*
Patients with first attack	13	9
Patients previously diagnosed		
Intermittent attacks	18	7
Continuous symptoms	10	16
Duration of disease (months)	5–456	7–120
Nutritional status (30)		
Good nutrition	25	12
Kwashiorkor like malnutrition	12	15
Marasmus	0	2
Mixed malnutrition	4	3
Previous surgery	0	4
Current drug therapy		
Patients untreated	5	10
Steroids alone	22	9
Sulphasalazine alone	6	3
Metronidazole alone	0	3
Steroids+sulphasalazine	6	2
Steroids+metronidazole	1	4
Steroids+metronidazole+sulphasalazine	1	1

TABLE II *Plasma fatty acids (FA) in ulcerative colitis (UC) as compared with controls*

%	*UC (n=41)*	*Controls (n=107)*	*p*
16:0*	26·9 (0·4)	25·2 (0·2)	0·0012
16:1†	1·7 [1·1–2·2]	1·7 [1·5–1·9]	0·4703
18:0†	8·2 [8·1–9·3]	10·5 [10·0–10·8]	<0·00001
18:1†	22·7 [20·5–24·8]	21·9 [20·9–22·8]	0·2870
18:2n6*	26·7 (0·7)	27·2 (0·4)	0·6293
18:3n3†	0·3 [0·0–0·5]	0·0 [0·0–0·0]	0·0143
18:3n6†	0·0 [0·0–0·0]	0·0 [0·0–0·0]	0·5597
20:2n6†	0·0 [0·0–0·3]	0·1 [0·0–0·3]	0·0711
20:3n6*	1·9 (0·1)	2·6 (0·1)	0·0001
20:4n6*	7·4 (0·3)	8·0 (0·2)	0·1320
20:5n3†	0·3 [0·0–0·5]	0·2 [0·0–0·4]	0·3414
22:6n3†	2·2 [1·9–2·8]	1·4 [1·3–1·6]	<0·00001
UNID*	131·8 (2·0)	131·5 (1·1)	0·9060

*Mean (SEM) Student's *t* test; †Median [95% CI]. Mann-Whitney U test; UNID=unsaturation index.

PLASMA FATTY ACID ASSAY

In all patients and healthy controls, a 5 ml venous blood sample for plasma fatty acid measurement was drawn after a 14 hour overnight fast at the same time that full clinical assessment was performed. Plasma was separated by centrifugation at 3000×*g* during five minutes and immediately frozen and stored at −50°C under nitrogen atmosphere.

The plasma obtained was treated with 5 ml of a chloroform:methanol (2:1 v/v) mixture containing 50 mg/l butylhydroxy-toluene, 1·5 ml 0·01 N HCl, and 50 µl $MgCl_2$ in water. The mixture was stirred for one minute in a tube mixer and then centrifugated at 3000×*g* for 10 minutes. The chloroform phase was separated by aspiration with a Pasteur pipette, and the aqueous phase was reextracted with 3 ml chloroform:methanol mixture. After centrifugation, chloroform phases were mixed and evaporated to dryness under nitrogen atmosphere.[31]

Saponification and methylation of fatty acids were immediately carried out, using 14% BF_3 in methanol according to the Morrison and Smith procedure.[32] Fatty acid methyl esters were quantified by gas liquid chromatography in a 5890A Hewlett-Packard chromatograph using a 30-m, wide bore column, 0·32 mm internal diameter, impregnated with SP-2330 as stationary phase. Initial oven temperature was 150° which was maintained for eight minutes; afterwards, it was increased at a rate of 3°/minute up to 210°C. The identification and quantification of fatty acid methyl esters was possible by using an external standard (Sigma Co, St Louis, Mo, USA). Individual response factors were calculated for each fatty acid.

Fatty acids from C14:0 to C22:6n3 were measured. Unidentified peaks accounted for less than 0·5% of total fatty acids. The desaturation index was calculated as previously described[33] according to the formula:

$$UNID = \Sigma \text{ (fatty acid percentage} \times \text{number of double bonds)}.$$

STATISTICAL ANALYSIS

For statistical analysis the Statistical Package for Social Sciences SPSS/PC+ (SPSS Inc, Chicago, Illinois, USA, 1985) was used.[34] Variables with normal distribution and homogeneous variance were compared by means of parametric tests, otherwise their non-parametric counterparts were used. To assess differences in plasma fatty acid percentages between patients and controls,

the Student's *t* test or Mann-Whitney U test were used, when necessary. One way analysis of variance with 'a posteriori' Scheffé test or Kruskall-Wallis one way analysis of variance by ranks were used, when necessary, to assess the influence of the severity of the disease upon fatty acid profile in these patients. When the Kruskall-Wallis test disclosed a significant p value, the Mann-Whitney U test was carried out in order to detect where the differences occur. Results are expressed as mean (SEM) or median and its 95% confidence interval[35] for parametric and non-parametric variables respectively.

Results

The clinical features of the 73 patients included in the study are detailed in Table I. Ulcerative colitis involved the entire colon in 21 patients, the left colon in 12, and was confined to the rectum in eight. Crohn's disease was ileocolic in 10 cases, involved only the small bowel in nine patients, and 13 patients had colonic disease.

TABLE III *Plasma fatty acids (FA) in Crohn's disease (CD) as compared with controls*

%	CD (n=32)	Controls (n=107)	p
16:0*	25·6 (0·3)	25·2 (0·2)	0·4372
16:1†	2·1 [1·6–2·8]	1·7 [1·5–1·9]	0·0725
18:0†	8·3 [7·8–9·4]	10·5 [10·0–10·8]	<0·00001
18:1†	23·4 [20·9–25·0]	21·9 [20·9–22·8]	0·0997
18:2n6*	25·8 (0·8)	27·2 (0·4)	0·1700
18:3n3†	0·7 [0·08–1·4]	0·0 [0·0–0·0]	<0·00001
18:3n6†	0·0 [0·0–0·3]	0·0 [0·0–0·0]	0·1954
20:2n6†	0·0 [0·0–0·2]	0·1 [0·0–0·3]	0·0340
20:3n6*	2·1 (0·1)	2·6 (0·1)	0·0041
20:4n6*	7·5 (0·3)	8·0 (0·2)	0·1920
20:5n3†	0·4 [0·0–0·7]	0·2 [0·0–0·4]	0·1725
22:6n3†	3·0 [1·7–3·8]	1·4 [1·3–1·6]	<0·00001
UNID*	136·2 (2·5)	131·5 (1·1)	0·0980

*Mean (SEM) Student's *t* test; †Median [95% CI]. Mann-Whitney U test; UNID=unsaturation index.

TABLE IV *Plasma fatty acids (FA) in ulcerative colitis. Influence of the activity of the disease*

%	Mild (n=12)	Moderate (n=19)	Severe (n=10)	p
16:0*	25·7 (1·1)	27·6 (0·3)	27·0 (0·6)	0·1605
16:1*	1·8 (0·2)	1·9 (0·3)	1·7 (0·3)	0·8801
18:0†	9·8 [8·2–12·0]	8·2 [7·6–9·5]	8·1 [7·2–10·0]	0·0253‡§
18:1†	18·8 [15·2–25·4]	22·7 [20·5–28·0]	25·1 [21·6–30·1]	0·0236‡§
18:2n6*	27·3 (1·3)	26·4 (1·2)	26·8 (1·4)	0·8845
18:3n3*	0·4 (0·1)	0·5 (0·1)	0·5 (0·2)	0·8647
18:3n6†	0·3 [0·0–0·8]	0·0 [0·0–0·0]	0·0 [0·0–0·2]	0·0013‡§
20:2n6†	0·2 [0·0–0·5]	0·0 [0·0–0·3]	0·0 [0·0–0·5]	0·2554
20:3n6*	2·7 (0·2)	1·6 (0·1)	1·3 (0·2)	0·0002‡§
20:4n6*	8·8 (0·4)	6·6 (0·4)	7·2 (0·4)	0·0243‡
20:5n3*	0·6 (0·1)	0·3 (0·1)	0·2 (0·06)	0·0622
22:6n3*	2·9 (0·1)	2·1 (0·2)	2·2 (0·1)	0·0648
UNID*	142·0 (3·0)	126·5 (3·1)	129·6 (2·2)	0·0031‡

*Mean (SEM). One way analysis of variance+Scheffé test; †Median [95% CI]. Kruskall-Wallis test+Mann-Whitney U test; †Mild *v* moderate; §Mild *v* severe; UNID=unsaturation index.

TABLE V *Plasma fatty acids (FA) in Crohn's disease. Influence of the activity of the disease*

%	Mild (n=15)	Moderate (n=11)	Severe (n=6)	p
16:0*	25·2 (0·4)	25·6 (0·6)	26·3 (1·2)	0·5419
16:1*	2·2 (0·3)	2·8 (1·0)	1·6 (0·5)	0·2123
18:0*	9·1 (0·3)	8·5 (0·4)	7·9 (0·5)	0·2045
18:1*	21·4 (1·0)	23·3 (0·8)	28·5 (2·5)	0·0064‡
18:2n6*	26·1 (1·2)	26·2 (1·3)	24·7 (1·9)	0·7929
18:3n3*	1·0 (0·2)	0·9 (0·2)	0·7 (0·3)	0·7644
18:3n6†	0·2 [0·0–0·4]	0·0 [0·0–0·3]	0·0 [0·0–1·1]	0·3943
20:2n6†	0·2 [0·0–0·4]	0·0 [0·0–0·05]	0·0 [0·0–0·5]	0·0640
20:3n6*	2·3 (0·2)	2·2 (0·2)	1·3 (0·2)	0·0641
20:4n6*	8·2 (0·5)	7·4 (0·4)	5·9 (0·5)	0·0443‡
20:5n3*	0·6 (0·1)	0·3 (0·1)	0·2 (0·1)	0·0620
22:6n3*	3·1 (0·3)	2·5 (0·4)	2·2 (0·5)	0·3760
UNID*	142·0 (3·0)	134·4 (3·3)	124·9 (7·8)	0·0355‡

*Mean (SEM). One way analysis of variance+Scheffé test; †Median [95% CI]. Kruskall-Wallis test+Mann-Whitney U test; ‡Mild *v* severe. UNID=unsaturation index.

Four patients with Crohn's disease who had previous operations (three colectomies and one ileocolectomy), were included because of relapsing disease.

PLASMA FATTY ACIDS

Plasma percentages of the different fatty acids in patients with ulcerative colitis and Crohn's disease are shown in Tables II and III.

ULCERATIVE COLITIS (Table II)

The most striking finding in plasma fatty acid profile in ulcerative colitis patients was the marked increase in n3 polyunsaturated fatty acids, both the essential precursor (α-linolenic acid (C18:3n3)) and the end product (docosahexaenoic acid (C22:6n3)).

In the n6 series, patients with ulcerative colitis showed low values of dihomo-τ-linolenic acid (C20:3n6), whereas values of the essential precursor (linoleic acid (C18:2n6)) and the main product (arachidonic acid (C20:4n6)) showed no differences when compared with controls.

Palmitic acid (C16:0) concentrations were significantly higher in ulcerative colitis patients than in healthy individuals. Stearic acid (C18:0) was significantly lower in ulcerative colitis than in controls. There were no differences in monoenoic fatty acids between patients and controls.

The unsaturation index did not show differences between patients with ulcerative colitis and controls.

CROHN'S DISEASE

The plasma fatty acid profile in Crohn's disease was similar to that found in ulcerative colitis (Table III). As in ulcerative colitis, a significant increase in n3 polyunsaturated fatty acids (α-linolenic acid (C18:3n3) and docosahexaenoic acid (C22:6n3)) and a decrease in plasma dihomo-τ-linolenic acid (C20:3n6), a long chain polyunsaturated fatty acids of the n6 series, was also observed.

When compared with healthy individuals, plasma concentrations of stearic acid (C18:0) was significantly decreased.

EFFECT OF THE ACTIVITY OF THE DISEASE

Fatty acid profile was related to the activity of the disease, both in ulcerative colitis (Table IV) and Crohn's disease patients (Table V). The plasma values of stearic acid (C18:0) and long chain n3 and n6 polyunsaturated fatty acids decreased stepwise as the disease became more severe. This only reached statistical significance for stearic acid (C18:0) and long chain n6 polyunsaturated fatty acids in ulcerative colitis and for arachidonic acid (C20:4n6) in Crohn's disease.

The decrease in plasma long chain polyunsaturated fatty acids associated to the increase of disease activity, was more marked in the n6 series (arachidonic and dihomo-τ-linolenic acid), especially in ulcerative colitis. It is remarkable that, in spite of the progressive fall in plasma docosahexaenoic acid values as inflammatory bowel disease became more severe, its mean

value always remained above the mean value of this n3 polyunsaturated fatty acid in healthy individuals. It is also noteworthy that in mild disease, concentrations of long n6 polyunsaturated fatty acids, especially arachidonic acid, also remained above those in healthy controls. The decrease in plasma long chain and highly unsaturated fatty acids in those patients with more severe disease, which resulted in a significant reduction of the unsaturation index, was partly counterbalanced by a significant increase in the percentage of oleic acid (C18:1).

Discussion

The most striking result of this study is the increased plasma concentrations of the precursor (α-linolenic acid) and the end product (docosahexaenoic acid) of the n3 polyunsaturated fatty acid series in active ulcerative colitis and Crohn's disease. In addition, low concentrations of dihomo-τ-linolenic (C20:3n6) acid were also found. When patients were grouped according to the severity of the attack, however, a stepwise fall in polyunsaturated fatty acids was observed as the disease became more severe. This was especially marked for long chain n6 polyunsaturated fatty acids in ulcerative colitis and Crohn's disease. It is remarkable that although concentrations of docosahexaenoic acid (C22:6n3) also tend to decrease stepwise as disease activity increased, their mean concentrations never reach values below that of healthy controls.

This pattern of plasma fatty acids suggests that, in active inflammatory bowel disease, increased polyunsaturated fatty acid biosynthesis might coexist with increased fatty acid consumption. The finding of high plasma n3 polyunsaturated fatty acids concentrations would support the first part of this hypothesis; that is, the increase in polyunsaturated fatty acid biosynthesis. This phenomenon would be particularly evident in this fatty acid series because n3 polyunsaturated fatty acids are preferential substrates for desaturases.[13 36] The fact that high concentrations of n6 fatty acids were also observed in patients with mild disease further supports the concept of an enhanced polyunsaturated fatty acid biosynthesis in inflammatory bowel disease.

The second part of the hypothesis – that is, the excessive consumption of fatty acids, might be supported by the stepwise fall of stearic acid (C18:0) and long chain polyunsaturated fatty acids, particularly those of the n6 series, observed as disease activity became more severe. Polyunsaturated fatty acid hypermetabolism may take place to meet the needs for cellular repair and to obtain energy (β-oxidation) as in other hypercatabolic states.[37 38] Another possible explanation for the more marked decrease in plasma n6, as compared with n3 polyunsaturated fatty acids, might be an increased synthesis of arachidonic acid derived eicosanoids in the intestinal mucosa in active disease.[7-12] It may be argued that low essential fatty acid intake could account for the diminished long chain polyunsaturated fatty acids in severe disease. Plasma concentrations of both essential fatty acids, linoleic (C18:2n6), and α-linolenic (C18:3n3), however, were not decreased even when disease was severe. To reinforce the suggestion of an enhanced polyunsaturated fatty acid synthesis, counterbalanced by hyperconsumption in active inflammatory bowel disease, studies have to be carried out in non-active patients.

A high intake of n3 fatty acids, especially of the essential α-linolenic acid, could be postulated as an explanation for the increased n3 polyunsaturated fatty acids in inflammatory bowel disease. This was not the case in our patients, however, as they were eating a standard western diet. This type of diet contains negligible amounts of long chain n3 fatty acids (less than 1% of the total fatty acids consumed).[39] In addition, these patients usually reduce their food intake when disease flares up. It could then be speculated that the high concentrations of α-linolenic acid (which is exclusively from dietary origin), might be the result of a negative feed back effect upon delta-6 desaturase activity, mediated by an excess of docosahexaenoic acid (C22:6n3), the final product of this series.[40-42]

The high concentrations of palmitic acid (C16:0) in ulcerative colitis suggest an enhanced lipolysis caused by increased energy requirements, as occur in other hypercatabolic states.[43 44] In this setting, it is difficult to explain the low plasma concentrations of stearic acid (C18:0). It might be speculated that this results in a diminished synthesis of stearic acid from palmitic acid (which would be preferentially oxidated) and/or an increased activity of delta-9-desaturase to produce oleic acid.

Two previous reports have assessed plasma polyunsaturated fatty acid pattern in patients with Crohn's disease. Both studies represent selected populations of patients with Crohn's disease as they included patients with either ileal resection[27] or malabsorption.[26] In contrast with our results, these studies describe a pattern of essential fatty acid deficiency, probably related to malabsorption. Severe malabsorption seldom occurs in Crohn's disease.

Two studies[45 46] have shown that in inflammatory bowel disease the concentrations of arachidonic acid (C20:4n6) in the inflamed colonic mucosa were increased. Moreover, in one[45] increased concentrations of docosahexaenoic acid (C22:6n3) were also found. These data are in agreement with our findings, and with the fact that plasma fatty acid pattern reflects the fatty acid composition of the tissues.[47]

The changes in n3 and n6 polyunsaturated fatty acid profile found in inflammatory bowel disease may be of relevance in the pathogenesis of the disease because they influence either tissue eicosanoid synthesis and the membrane lipid composition of the immunocompetent cells.[48] It has been demonstrated that in vitro manipulation of fatty acid composition of lymphocytes can alter immune functions, such as cytotoxicity, antibody response, or cell to cell recognition.[48 49] In this context, the similar polyunsaturated fatty acids pattern found in ulcerative colitis and Crohn's disease suggests that both diseases might share a common pathogenic mechanism. It would be of interest to know whether this plasma fatty acid pattern, not previously

reported in other disease states,[50] is exclusive to inflammatory bowel disease or also occurs in other autoimmune conditions.

Based on the fact that eicosapentaenoate derived eicosanoids have attenuated proinflammatory activity as compared with arachidonate derived compounds, dietary n3 polyunsaturated fatty acid supplements (fish oil) have been successfully used in experimental animal models of inflammation[21] and in patients with rheumatoid arthritis.[22] According to this hypothesis, they have been administered in inflammatory bowel disease patients, but the results of various clinical trials are controversial.[23-25] Our finding of high plasma n3 polyunsaturated fatty acid concentrations in active inflammatory bowel disease raises some doubts on the use of high doses of n3 polyunsaturated fatty acids in the treatment of inflammatory bowel disease.

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