RESEARCH ARTICLE

Relationship between plasma free amino acid profiles and changes in Crohn's disease activity index after administration of an elemental diet in patients with Crohn's disease

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Abstract:

Purpose: We aimed to elucidate the relationship between plasma free amino acid profiles and changes in the Crohn's disease activity index (CDAI) among patients with Crohn's disease (CD) after administration of an elemental diet (ED).
Patients and methods: We measured fasting plasma concentrations of free amino acids in 5 patients with CD and evaluated the relationship between amino acid concentration and disease activity at 4 weeks after administration of an ED.
Results: Concentrations of valine, lysine, tyrosine, and glutamic acid were significantly increased after administration of an ED. Significant correlations were noted between changes in CDAI scores and valine concentrations. Tryptophan concentrations also exhibited a strong correlation with CDAI scores.
Conclusion: In patients with CD, plasma concentrations of valine and tryptophan appear to be associated with disease activity following treatment with an ED.

Keywords: Crohn's disease, amino acids, elemental diet, CDAI

Introduction

Malnutrition is one of the most significant problems in patients with Crohn's disease (CD), necessitating nutritional support for modulating intestinal inflammation[1,2]. Amino acids (AAs) are required for the production of energy and other biological functions. Specific AAs belonging to the group of essential amino acids (EAAs), such as glutamine (Gln) and arginine (Arg), exhibit immunomodulatory effects during metabolic stress, especially when the gut is involved in systemic inflammation. Some AAs, such as glycine (Gly), histidine (His), cysteine (Cys), and taurine (Tau), exhibit anti-inflammatory properties in intestinal epithelial cells[3]. The anti-inflammatory activities of certain AAs have recently been reported[4,5], and antagonistic effects of AAs on intestinal inflammation have also been demonstrated[6-15]. AA metabolism and synthesis are closely linked to various body systems, including the endocrine system, immune system, and muscular system. However, AA metabolism is significantly altered during disease states. The immunomodulatory effects and cell signaling functions of AAs have been extensively investigated, and play a critical role in various aspects of health and disease.

Levels of essential (leucine [Leu], lysine [Lys], and valine [Val]), semi-essential (Arg and Gln), and non-essential (serine [Ser]) amino acids are known to be decreased in CD subjects compared to control subjects[16].

In our previous study, we analyzed the plasma free amino acid (PFAA) profiles in patients with CD, with an emphasis on correlations with disease activity. Results of this study showed that the concentrations of 5 amino acids, namely Val, methionine (Met), Leu, His and tryptophan (Trp), were significantly correlated with Crohn's disease activity index (CDAI) scores in patients with CD, which reflects the degree of inflammation. These AAs all belong to the class of EAAs, which are supplied in the diet. Furthermore, significant correlations were shown between CDAI scores and a certain proportion of EAAs and nonessential amino acids (NEAAs) in patients with CD. Nutritional deficiencies in patients with active CD are the result of insufficient intake, malabsorption and protein-losing enteropathy, as well as metabolic disturbances induced by chronic disease[17].

Gln concentrations are also correlated with CDAI scores in CD[17]. Gln is an immunomodulatory agent in intestinal epithelial cells that protects the function of the intestinal mucosal barrier, and also serves as the basic nutritional element for cellular immune function[18]. Gln administration failed to produce obvious biochemical or clinical benefits in patients with active inflammatory bowel disease (IBD)[19]. Plasma His and Trp concentrations were significantly lower in patients with IBD than in healthy controls[20].

These observations suggest plasma AA concentrations are closely associated with disease activity in CD. However, PFAA profiles have not been well investigated in patients with CD after administration of an elemental diet (ED). The goal of this study was to elucidate the relationship between PFAAs and CDAI after administration of an ED.

Material and methods

PATIENTS

A total of 5 CD patients with CDAI 150 or above were included in this study (1 female, 4 males; mean age 33.3 years; 2 ileo-colonic type, 2 ileal type, 1 colonic type). The mean disease duration was 10.3 years (range, 3-30 years).

All patients were treated with oral mesalamine (750-3,000 mg/day). Two patients with the ileo-colonic type and 1 patient with the colonic type also received oral prednisone (PSL) (5-25 mg/day). Two patients with the ileo-colonic type, 2 patients with the ileal type and 1 patient with the colonic type were given oral azathioprine (AZA) (50 mg/day). In addition, 2 patients with the ileo-colonic type and 1 patient with the ileal type were treated with anti-TNF-α agents. All patients were given the same dosages of medicines both before and after administration of an ED.

METHODS

Fasting plasma amino acid concentrations and CDAI scores were measured before and at 4 weeks after oral administration of 300-600 Cal/day of an ED (Elental®). Patients' CDAI scores were evaluated at the time of blood sampling[21]. Plasma samples for AA analysis were obtained in the morning before breakfast using EDTA as an anticoagulant. Changes in transferrin, prealbumin, albumin and BMI were examined as a nutritional index.

Fasting plasma concentrations of the 20 AAs—threonine (Thr), Val, Met, isoleucine (Iso), Leu, phenylalanine (Phe), His, Trp, Lys, aspartic acid (Asp), Ser, asparagine (Asn), glutamic acid (Glu), Gln, proline (Pro), Gly, alanine (Ala), Cys, tyrosine (Tyr), and Arg—were measured by high-performance liquid chromatography (HPLC). The concentrations of total amino acids (TAAs), EAAs and NEAAs were subsequently calculated.

The study protocol was approved by the Institutional Review Board at Iwate Medical University and the study was performed in accordance with the Declaration of Helsinki.

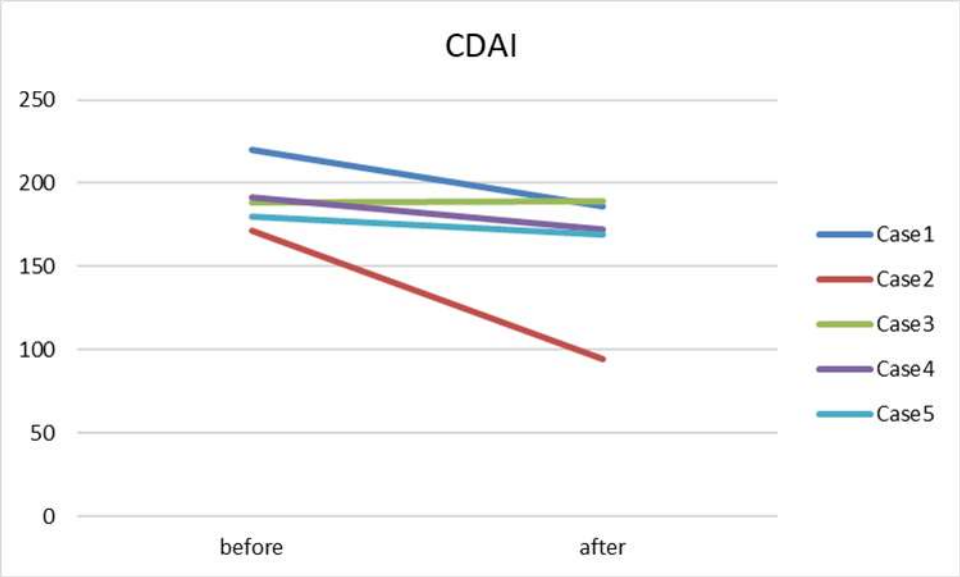
Statistical analyses

Within-group comparisons were analyzed using the paired t test. Correlations were evaluated by Pearson's correlation coefficient test using BellCurve for Excel. A *P* value <0.05 was considered statistically significant.

Results

CDAI: CDAI scores were not significantly different before and at 4 weeks after administration of an ED (Figure 1).

Figure 1: CDAI scores before and after administration of an ED in patients with CD.
CDAI scores were not significantly different before and at 4 weeks after administration of an ED.



Abbreviations: CDAI; Crohn's disease activity index, ED; elemental diet, CD; Crohn's disease.

Nutrition index: Transferrin, prealbumin, albumin and BMI were not significantly different before and after administration of an ED.

Amino acids: Concentrations of Val, Lys, Glu, Tyr were significantly increased after administration of an ED, whereas concentrations of other AAs were not significantly different before and after administration of an ED (Table 1).

Table 1: Comparison of concentrations of AAs before and after administration of an ED in patients with CD.

AAs (nmol / mL)	before	after	*P*-value	normal range
EAAs				
Thr	94.2 [82.5-123.7]	116.0 [86.9-154.9]	NS	[66.5-188.9]
Val	176.9 [156.2-208.7]	218.4 [184.3-267.6]	<0.05	[147.8-307.0]
Met	24.0 [21.1-29.5]	23.9 [23.0-26.0]	NS	[18.9-40.5]
Iso	69.0 [69.1-73.7]	76.4 [70.3-93.3]	NS	[43.0-112.8]
Leu	100.2 [80.9-128.4]	118.2 [95.6-151.8]	NS	[76.6-171.3]
Phe	52.0 [49.8-57.4]	54.5 [54.5-56.0]	NS	[42.6-75.7]
His	64.7 [64.6-71.3]	65.1 [65.4-73.5]	NS	[59.0-92.0]
Trp	38.6 [19.3-53.6]	46.4 [33.4-63.8]	NS	[37.0-74.9]
Lys	133.4 [127.4-145.6]	156.8 [153.8-168.8]	<0.05	[108.7-242.2]
NEAAs				
Asp	4.5 [3.3-6.1]	4.9 [4.0-6.3]	NS	[<2.4]
Ser	111.3 [99.6-124.6]	116.4 [115.7-126.8]	NS	[72.4-164.5]
Asn	41.8 [38.7-47.7]	43.5 [40.6-47.3]	NS	[44.7-96.8]
Glu	38.0 [35.7-46.5]	57.1 [36.3-81.2]	<0.05	[12.6-62.5]
Gln	494.4 [435.5-535.1]	490.5 [493.5-515.9]	NS	[422.1-703.8]
Pro	185.6 [157.8-244.2]	176.1 [147.9-222.9]	NS	[77.8-272.7]
Gly	229.7 [201.5-254.0]	229.1 [207.9-247.4]	NS	[151.0-351.0]
Ala	344.3 [262.1-445.8]	366.5 [287.8-482.4]	NS	[208.7-522.7]
Cys	10.0 [6.8-14.4]	9.6 [7.6-12.5]	NS	[13.7-28.3]
Tyr	48.0 [42.5-58.5]	55.1 [53.5-63.4]	<0.05	[40.4-90.3]
Arg	79.2 [76.1-89.5]	77.4 [72.5-81.3]	NS	[53.6-133.6]
TAAs	2514.7 [2242.0-2829.8]	2708.4 [2569.4-2934.8]	NS	[2068.2-3510.3]
NEAAs	1761.8 [1615.4-1948.2]	1832.7 [1709.7-1953.7]	NS	[1381.6-2379.4]
EAAs	752.9 [627.6-881.6]	875.7 [721.6-1039.1]	NS	[660.0-1222.3]
BCAAs	346.0 [297.2-410.6]	412.9 [350.2-512.6]	NS	[265.8-579.1]

Abbreviations: AAs; amino acids, EAAs; essential amino acids, NEAAs; non-essential amino acids, TAAs; total amino acids, BCAAs; branched-chain amino acids, NS; not significant.

Relationship between changes in CDAI scores and amino acids concentrations before and after administration of ED: Significant correlations were noted between changes in CDAI scores and concentrations of Val (r=-0.89). Trp concentrations were also strongly correlated with CDAI scores (r=-0.84). No significant correlations were observed between CDAI scores and concentrations of any other AAs (Table 2).

Table 2: Relationship between changes in CDAI scores and AAs concentrations before and after administration of ED in patients with CD.

AAs		
	r	*P*-value
EAAs		
Thr	0.03	NS
Val	-0.89	0.02
Met	-0.42	NS
Iso	-0.81	NS
Leu	-0.60	NS
Phe	-0.54	NS
His	0.03	NS
Trp	-0.84	0.07
Lys	-0.38	NS
NEAAs		
Asp	0.71	NS
Ser	0.51	NS
Asn	0.31	NS
Glu	-0.21	NS
Gln	-0.15	NS
Pro	0.43	NS
Gly	-0.54	NS
Ala	0.04	NS
Cys	-0.74	NS
Tyr	0.11	NS
Arg	-0.43	NS

TAAs	-0.42	NS
NEAAs	-0.08	NS
EAAs	-0.66	NS
BCAAs	-0.78	NS

Abbreviations: CDAI; Crohn's Disease activity index, ED; elemental diet, AAs; amino acids, EAAs; essential amino acids, NEAAs; non-essential amino acids, TAAs; total amino acids, BCAAs; branched-chain amino acids, NS; not significant.

Discussion

AA-based diets were shown to improve intestinal permeability in patients suffering from CD[22]. Since dietary intervention as a treatment for IBD is less invasive compared to conventional medical approaches, prophylactic and nonpharmaceutical treatment of IBD is desirable[23].

The anti-inflammatory and antioxidative properties of functional foods, such as AAs[24,25], were shown to have numerous beneficial effects in preclinical colitis models by modulating the immune system and reducing oxidative stress in human subjects and animals.

The functionalities of AAs play an important role in various aspects of health and disease. The vulnerability of AAs to oxidation by reactive oxygen species (ROS) primarily depends on the properties of their side chains. All AAs are theoretically oxidizable, but the most oxidizable include those with nucleophilic sulfur-containing side chains, such as Cys and Met, or aromatic side chains like Trp, Tyr and Phe[26]. H_2O_2-stimulated oxidative stress in Caco-2 intestinal epithelial cells was shown to be inhibited after pre-treatment with Cys, Val, Iso, Leu, Trp, His, Lys and Ala[27,28].

In this study, we measured PFAA profiles of CD patients after administration of an ED. Concentrations of Val, Lys, Glu and Tyr were found to be increased after administration of an ED. Correlations were noted between variability of CDAI score and Val and Trp concentrations.

Concentrations of His, Trp, Val and Met increased after treatment with an ED in patients with clinical remission; ED was effective in improving disease activity, nutritional status, and increased plasma amino acid levels of His, Trp, Val and Phe, and thus may be particularly effective for poorly nourished patients with CD who have not previously undergone treatment with an ED[29].

Supplementation of L-Trp not only ameliorated clinical symptoms and increased weight gain, but also improved histological scores and decreased the expression of proinflammatory cytokines in a porcine model of DSS colitis[30,31]. Concentrations of AAs changed depending on the degree of colitis in DSS-treated mice, and serum levels of Gln, Trp, Tyr, Asn and Gly were significantly lower than in control mice[32]. Active CD is associated with depression of serum Trp[33]. Trp metabolism has recently been highlighted as an immunological regulator[34-36], and supplementation of His and Trp has been suggested as a therapeutic strategy for IBD[37]. AA-based EDs would be useful by virtue of their low antigenicity[38], resulting in a reduction in production of mucosal cytokines, such as IL-1, IL-6, IL-8 and TNF-α[39]. Trp has also been

shown to have Ca^{2+} sensing receptor (CaSR) agonistic activity[40], and Trp supplementation inhibited IL-8 production from inflamed intestinal epithelial cells in a CaSR dependent manner[23]. Further, Trp catabolism through the kynurenine metabolic pathway is involved in modulating homeostasis of the immune system, by activating the tryptophan catabolic enzyme indoleamine 2,3-dioxygenase (IDO) [41], and inducing apoptosis of Th1 cells. Trp supplementation reduced gut permeability, expression of proinflammatory cytokines, and increased expression of the apoptosis initiators caspase-8 and Bax[42]. Trp is a precursor of serotonin (5-hydrotryptamine) [31], and low levels of serum Trp can affect serotonin biosynthesis, resulting in impaired quality of life and depression. Trp deficiency may result in immunodeficiency in the presence of persistent immune activation[43]. Trp was also associated with increased IL-22 and STAT3 expression and protection of epithelial integrity[44]. Thus, Trp may be a promising candidate for the treatment of IBD.

Glu is active as an excitatory neurotransmitter[45], participates in enterocyte oxidative metabolism[46], is a precursor of various polyamines, AAs, and glutathione (GSH) [47], and regulates oxidative reactions[48] and metabolic pathways[47]. Glu may be an adjuvant IBD treatment with broad application[49]. In an IBD rat model, microinjection of Glu into the hypothalamic paraventricular nucleus (PVN) promoted cell proliferation and increased antioxidant levels, and inhibited apoptosis and expression of the proinflammatory factors TNF-α and IL-1[49]. The mechanism of action of Glu may depend on binding to a glutamate receptor on the membrane of PVN neurons.

There are several limitations associated with the present study. First, we measured AA profiles in a small number of CD patients; however, we believe that the results of our study will be useful to inform provisional supplementation for patients with active CD. The efficacy associated with supplementation of those specific AAs that are depleted in active CD should be evaluated. Second, we investigated AA levels at 4 weeks after administration of an ED. Future studies should investigate the AA profiles in a larger population of CD patients after longer durations following administration of an ED.

Conclusion

In conclusion, plasma concentrations of Val and Trp are closely associated with disease activity in patients with CD after administration of an ED.

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Disclosure

The author reports no conflicts of interest in this work.

Declarations

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Ethics approval and consent to participate

The study proposal was reviewed and approved by the Human Ethics Review Committee of Iwate Medical University. Written informed consent was obtained from each patient prior to enrollment.

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