ELSEVIER

e-SPEN,
the European e-Journal
of Clinical Nutrition
and Metabolism

http://intl.elsevierhealth.com/journals/espen

ORIGINAL ARTICLE

High-dose oral supplementation of antioxidants and glutamine improves the antioxidant status in patients with Crohn's disease: A pilot study☆

Cornelia Roggenbuck [a], Frank Lammert [b], Heiner K. Berthold [c], Thomas Giese [d], Andreas Stallmach [e], Peter Stehle [a], Sabine Ellinger [a,*]

[a] *Department of Nutrition and Food Science - Nutritional Physiology, Rheinische Friedrich-Wilhelms-University of Bonn, Germany*
[b] *Department of Internal Medicine I, University Hospital Bonn, Germany*
[c] *Medical Faculty, Clinical Pharmacology, University Hospital Bonn, Germany*
[d] *Institute for Immunology, Ruprecht-Karls-University Heidelberg, Germany*
[e] *Department of Gastroenterology, Hepatology and Infectious Diseases, Clinic of Internal Medicine II, Friedrich-Schiller-University Jena, Germany*

Received 6 December 2007; accepted 25 June 2008

KEYWORDS
Crohn's disease;
Antioxidants;
Glutamine;
Oxidative stress;

Summary
Background & aims: Since oxidative stress stimulates inflammation, high-dose supplementation of antioxidants (AOX) and glutamine (GLN) may reduce oxidative stress and mucosal inflammation and may increase quality of life (LQ) in patients with Crohn's disease (CD).

Abbreviations: AOX, antioxidant micronutrients; CD, Crohn's disease; CDAI, Crohn's disease activity index; GLN, L-glutamine; GSH, glutathione; 8-OHdG, 8-hydroxydesoxyguanosine; IBD, inflammatory bowel disease; IL-8, interleukin-8; MRP-14, myeloid related protein-14; ONS, oral nutritional supplement; ROS, reactive oxygen species; SGA, subjective global assessment; TEAC, Trolox equivalent antioxidant capacity.

☆ The data of this study were partly presented at the 28th Congress of the European Society of Parenteral and Enteral Nutrition (ESPEN), Istanbul, Turkey, October 2006 (CR and SE, poster and oral presentation), and at the 44th Scientific Conference of the German Nutrition Society (DGE), March 2007, Halle/Saale, Germany (CR, oral presentation).

* Corresponding author. IEL - Nutritional Physiology, University of Bonn, Endenicher Allee 11–13, 53115 Bonn, Germany. Tel.: +49 228 73 3814; fax: +49 228 73 3217.
E-mail address: ellinger@uni-bonn.de (S. Ellinger).

1751-4991/$ - see front matter
doi:10.1016/j.eclnm.2008.06.012

Mucosal inflammation; intervention

Methods: Within a bicentric pilot study, six patients with CD (median CDAI 139) ingested 2 × 200 ml/day of an oral nutritional supplement (ONS) rich in AOX and GLN for 4 weeks in additional to their basic medication. Before and after intervention, antioxidant status and antioxidant capacity were determined in plasma and markers of oxidative stress in plasma and leukocytes. Glutathione and transcripts of interleukin-8 (IL-8) and myeloid related protein-14 (MRP-14) were measured in the gut mucosa and LQ was determined by the inflammatory bowel disease questionnaire.
Results: Vitamin C, E, β-carotene, selenium and antioxidant capacity increased (all $p < 0.05$). Peroxides decreased ($p = 0.043$), whereas further markers of oxidative stress did not change. Glutathione of the inflamed mucosa increased ($p = 0.043$), but IL-8- and MRP-14-mRNA were unchanged. Overall, LQ increased significantly ($p = 0.027$).
Conclusions: An ONS rich in AOX and GLN may improve antioxidant status both in plasma and in the inflamed mucosa in patients with CD. Although the effects on oxidative stress and mucosal inflammation are not clear, these results encourage placebo-controlled studies.

Introduction

There is a growing body of evidence that reactive oxygen species (ROS) are involved in the pathogenesis of Crohn's disease (CD).[1] During chronic bowel inflammation, ROS produced by activated neutrophils infiltrate the intestinal wall, thereby stimulating the expression of inflammatory cytokines[2] and leading to mucosal damage.[3,4] In addition, cross-sectional studies have shown that products from lipid peroxidation in plasma[5–9] and expiration volume[8] are increased in patients with CD compared to healthy controls and correlate with the inflammation status in patients with CD.[6]

Decreased plasma[7,8,10–13] and mucosal[4,14,15] concentrations of antioxidant micronutrients (AOX) compared to healthy subjects may further aggravate the chronic inflammation in CD patients. Consequently, the supply of AOX may be a promising countermeasure within an adjuvant nutrition therapy. A first intervention study has shown that supplementation of a supraphysiological dose of vitamin C (1000 mg/day, 11–14 times the RDA) and vitamin E (800 IU/day, 35 times the RDA) can reduce markers of lipid peroxidation in plasma (peroxides, F2-isoprostanes) and in expiration volume (pentane output).[16] Whether this effect is limited to vitamin C and E or whether a more complex mixture of AOX would further improve the clinical situation is not known.

L-Glutamine (GLN) is the major metabolic fuel for enterocytes and leukocytes which has shown to stimulate their proliferation and to maintain mucosal integrity in several studies.[17] Ingestion of GLN reduced the secretion of inflammatory cytokines (e.g. interleukin-8 (IL-8)) from cultured duodenal biopsies obtained from healthy volunteers,[18,19] indicating that GLN supplementation may reduce mucosal inflammation in patients with inflammatory bowel disease (IBD).[18,19]

Hence, the primary aim of this bicentric pilot study was to investigate the effects of a 4-week ingestion of an oral nutritional supplement (ONS) containing a mixture of nutritive AOX and the gut-specific substrate GLN on biomarkers of antioxidant status and oxidative stress in patients with CD. In addition, the influence on mucosal inflammation and disease activity should be determined.

Subjects and methods

Subjects and study design

Between January 2005 and March 2006, eight adult CD patients (18–50 years) free of liver disease (medical history) were recruited in two German clinical centres (Marienhospital Essen; Department of Internal Medicine I, University Hospital Bonn). Exclusion criteria were: cortisone intake more than 50 mg/day, antibiotic treatment, use of micronutrient supplements or probiotics, and pregnancy. At study entry, patients were weighed and the nutrition status was determined using the subjective global assessment (SGA).[20] Disease activity was judged by the Crohn's Disease Activity Index (CDAI) before and after intervention.

The participants were instructed to consume 200 ml of the ONS (Fresenius Kabi, Bad Homburg, Germany; composition see Table 1) twice daily in addition to their diet for 4 weeks. Patients were asked to document the intake of the ONS in a patient diary to assess the compliance as the percentage of the ingested to the target dose. Non-compliance was defined as ingestion of <80% of target for 4 weeks. Non-compliant participants were excluded from the study evaluation.

Table 1 Composition of the oral nutritional supplement (400 ml)

Antioxidants	Ingredients (400 ml)
Vitamin C	1500 mg
Vitamin E	500 mg
β-Carotene	10 mg
Zinc	20 mg
Selenium	300 μg
Glutamine (as dipeptides)	30 g
Carbohydrates[a]	15 g
Energy[b]	250 kcal

[a] From maltodextrin (64%), saccharose (24%) and fructose (12%).
[b] From dipeptides and carbohydrates.