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PRELIMINARY REPORTS: IMPROVEMENT IN MUCOSAL INTEGRITY IN IBD PATIENTS AND REDUCTION IN GI SYMPTOMS IN HIV PATIENTS WITH HYDROLYZED WHITE FISH

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ABSTRACT

Dietary peptides are known to have biological importance beyond their nutritive value as protein, influencing structural, immune, and gastrointestinal functions. Protein balance studies performed in patients with inflammatory bowel disease (IBD) indicate better nitrogen balance with peptide-based diets than with whole-food diets, which are in turn better than amino acid-based diets. However, no studies have examined the use of supplemental peptides in improving gut epithelial permeability and associated symptom relief. In a preliminary investigation, supplementation with a dietary bioactive peptide supplement prepared from hydrolyzed white fish was studied in two distinct populations in separate trials. In the first study, 15 IBD patients assessed to have gut mucosal hyperpermeability by a urine test utilizing lactulose and mannitol ratios were given either 3g per day of the fish peptide supplement or a placebo for 6 weeks, followed by a second permeability test and symptom assessment scoring. Results with the IBD patients taking the supplement showed a trend towards improvement in both intestinal permeability and symptom assessment versus controls. We then hypothesized that if GI symptoms resulting from current recommended HIV therapy are associated with a similar inflammatory mechanism, as suggested, these patients would also respond favorably to the peptide supplementation. Accordingly, a second population of 23 HIV-infected males experiencing GI side effects on highly active antiretroviral therapy (HAART) were given either 3g per day of the fish peptide supplement or a placebo for 5 months, with symptoms assessed before and after the treatment period. In the HIV patients, the number of GI symptoms collec-

tively reported as decreased in the supplement group was significantly greater than the number of symptoms collectively reported as decreased in the control group. These bioactive peptides appear to have a possible dual function in HIV patients: controlling intestinal permeability that may result from long-term use of HAART and reducing GI symptoms, which may result in increased HAART compliance and improved treatment outcome.

BACKGROUND

Inflammatory bowel disease (IBD) is a chronic inflammatory condition generally categorized as either ulcerative colitis (UC) or Crohn's disease, based on established disease criteria and the location of the inflammation. Recommended medical treatment includes corticosteroid therapy, as well as nutritional interventions, such as elemental peptide diets and micronutrient supplementation.¹ Up to 85% of patients hospitalized with IBD have protein-energy malnutrition, which can inhibit response to therapy and limit wound and fistula healing.^{2,3} Nutritional therapy for IBD has traditionally consisted of elemental or oligopeptide diets with the theory of "putting the gut at rest," while supplementing with easily digestible, hypoallergenic nutrients.⁴ Oligomeric (small-chain peptides or hydrolyzed protein) supplementation is preferred over monomeric (free amino acid) or polymeric (whole protein) supplementation, based on evidence of increased biological value (in starved rats)⁵ and increased nitrogen balance in Crohn's patients.⁶ Glutamine-supplemented polymeric diets have demonstrated no benefit in

Crohn's disease.⁷ Specific nutrients believed to benefit patients with IBD include fish oils, which provide anti-inflammatory omega-3 fatty acids that are shown to reduce the rate of relapse frequency in IBD;⁸ short-chain fatty acids, like butyrate;⁹ and other trophic factors, such as dietary peptides.¹⁰ Bioactive dietary peptides act locally on the mucosal barrier, as well as cross into the systemic circulation.

Seacure, used in both trials, is a commercially available hydrolyzed fish protein supplement (manufactured by Proper Nutrition, Inc.) that provides peptides and amino acids, predominantly glutamine, in an approximate ratio of 60:40.

Both UC and Crohn's disease are associated with intestinal epithelial hyperpermeability, although the evidence is more established for the latter.¹¹ Successful treatment of Crohn's with elemental diets is demonstrated by a reduction in intestinal permeability (IP), and normal IP in IBD patients has prognostic implications and may predict well-being.¹²

When properly used in HIV management, highly active antiretroviral therapy (HAART) can prevent opportunistic infections (OIs), maintain weight, improve viral counts, delay the progression to AIDS, and extend life.^{13,14} However, GI complaints, such as diarrhea, affect an estimated 50-70% of HIV patients on HAART.^{15,16} Such events can limit compliance to HAART, which leads to sub-therapeutic drug levels, viral mutations against HAART agents, and failure to achieve or maintain viral suppression.¹⁷ The management of GI issues in HIV patients on HAART relates to quality of life and may play a role in compliance with medications and treatment outcome.

A relationship appears to exist between HIV and the health of the GI tract, including increased intestinal permeability, impaired gut-associated immune function, and oxidative stress,¹⁸ although the particular inflammatory and functional changes in HIV-related intestinal disease remain unclear.¹⁹

MATERIALS AND METHODS

Study 1: IBD

The study design was randomized, double-blind, and placebo-controlled, with final evaluation at the end of 6 weeks of treatment. The treatment group (n=7) received fish peptide supplement, while the placebo group (n=8) received barley placebo, 2 x 500mg capsules TID. The study population consisted of adult patients with Crohn's disease or UC who had been on the same dose of mesalamine, sulfasalazine, or prednisone for at least 3 months, or had not taken prednisone for at least 14 days. **[AU: Should it be "a" fish peptide supplement? Also, what is JEA1?]**

Intestinal barrier function has implications for the etiology and pathogenesis of IBD, and tests of intestinal perme-

ability are useful in screening, assessing treatment, and predicting the prognosis.^{20,21} IP is most commonly assessed by differential urinary excretion of lactulose and mannitol.¹⁹ Lactulose is a larger molecule than mannitol, such that a relative increase in the presence of lactulose signifies hyperpermeability. Successful treatment of IBD is matched by a significant reduction in the lactulose:mannitol ratio, indicative of improved permeability.²⁰ Testing was conducted by Great Smokies Diagnostic Laboratories, Asheville, NC.

Disease severity was assessed using the Crohn's Disease Activity Index,²¹ and each patient completed before and after global symptom assessments. According to practice guidelines developed under the auspices of the American College of Gastroenterology, patient and clinician global assessments correlate well to IBD activity for use in clinical research.²²

IP and symptom scores were analyzed for treatment and control subjects separately by T-tests. A P-value of <0.05 was required for statistical significance. In order to standardize starting points and analyze test patients against control patients, percent changes in scores were calculated [% change = (score1-score2)/score1x100%], with analysis by ANOVA.

Study 2: HIV

The site for the study was a large urban private medical practice with approximately 400 HIV-positive patients. Thirty-two patients were selected over a 2-month period, based on the following inclusion criteria: HIV-positive, ability to provide informed consent, ability to adhere to daily supplement regimen, life expectancy of at least 6 months, age greater than 18 years, absence of any OIs, compliance with uninterrupted HAART for at least 6 months, and viral load of less than 50 copies/mL; and the following exclusion criteria: female gender, life expectancy of less than 6 months, opportunistic malignancy requiring systematic chemotherapy within 30 days of study entry, the presence of any OIs, or concurrent use or prior use of anabolic agents/appetite stimulants/corticosteroids within 30 days of study entry.

The outcome-based study design was randomized, double-blind, and placebo-controlled. Patients were evaluated monthly for a total study duration of 5 months. The treatment group (n=18) received the fish peptide supplement, while the placebo group (n=14) received the barley placebo, 2 x 500mg capsules TID. Patient questionnaires and clinician interviews were used to assess changes in intestinal symptoms and quality-of-life issues, while routine blood testing was used to identify any changes in disease status. The use of questionnaires for evaluating quality-of-life issues related to HAART and nutritional support has been documented.²³ Interviews and blood tests were conducted monthly. Statistical analysis was performed using T-tests,

assuming normal distributions and equal variances. A P-value of <0.05 was required for statistical significance.

RESULTS

Study 1: IBD

We observed a trend toward improvement in both IP (Figure 1, $p=0.07$) and symptom scores (not shown) in patients receiving fish peptides, although results failed to reach statistical significance. No such trend toward improvement in IP was identified in control patients ($p=0.41$). The percent changes were 76% improvement in patients receiving fish peptides and 32% improvement in controls (Figure 2), again not statistically significant but indicative of a trend towards increased improvement in patients receiving fish peptides versus control patients.

Study 2: HIV

The mean age of patients was 43.9 years (30-64). Five patients in the fish peptides group were lost to follow-up, one patient withdrew from the study prior to completion, and one patient died from Hepatitis B two months into the study. Two patients in the placebo group withdrew prior to completion. Twenty-three patients completed the study (test $n=11$, control $n=12$) and were used for data analysis. Blood profiles were monitored, and remained stable for all patients.

As seen in Table 1, there was no difference between the 2 study groups in the number of patients reporting symptoms at baseline ($p=0.911$). At 5 months (Table 2), the number of symptoms collectively reported as decreased in the fish peptides group was significantly greater than the number of symptoms collectively reported as decreased in the control group ($p=0.0479$). Further, all 11 patients receiving fish peptides, and 2 of 12 patients receiving placebo, felt better overall.

DISCUSSION

We observed a trend (not significant) towards improvement in IP and symptoms in IBD patients, as well as a significant decrease in total GI symptoms in HIV-positive males on HAART when supplemented with the fish peptides. We were limited by a small sample size, which may have been responsible for the failure to reach significance in IP testing. In the first study, we also observed that patients clearly identified by standard measures as having IBD did not always exhibit abnormal IP scores, making it difficult to recruit a suitable number of subjects. As a result, HIV patients evaluated in the second study were not assessed for changes in IP, greatly limiting our ability to draw clear conclusions.

Clinicians must recognize that, to the patient, the GI effects of HAART are like a disease unto themselves. The

management of GI issues in HIV treatment may relate not only to quality of life, but also to HAART compliance, and thus contribute to viral suppression and extend life. Supplementation with these fish peptides may control IBD-like intestinal permeability that results from long-term HAART use, and appears to reduce the GI side effects of HAART, which may result in increased compliance and improved treatment outcome.

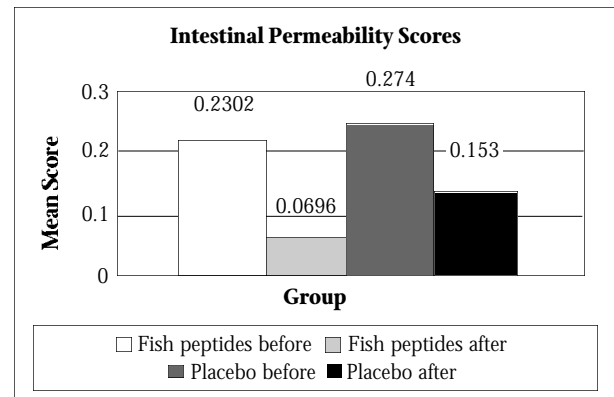


FIGURE 1
INTESTINAL PERMEABILITY SCORES BEFORE AND AFTER 6 WEEKS OF SUPPLEMENTATION WITH FISH PEPTIDES OR PLACEBO

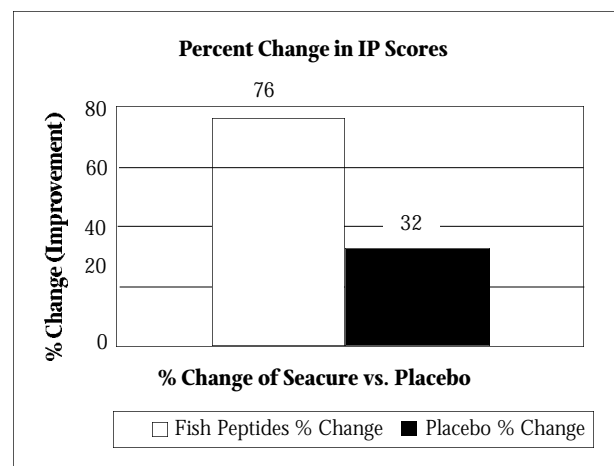


FIGURE 2
PERCENT CHANGE IN INTESTINAL PERMEABILITY SCORES AFTER 6 WEEKS OF SUPPLEMENTATION WITH FISH PEPTIDES OR CONTROL

TABLE 1
ANALYSIS OF STUDY RESULTS—BASED ON 11 PATIENTS
IN FISH PEPTIDE GROUP AND 12 PATIENTS IN
PLACEBO GROUP AT THE START OF THE STUDY

Symptom	Number of Fish peptide patients reporting symptom at baseline	Number of Placebo patients reporting symptom at baseline
Diarrhea	7	7
Nausea	4	4
Constipation	2	2
Bloating	7	6
Fatigue	9	9
MEAN	5.8±2.8	5.6±2.7

TABLE 2
ANALYSIS OF STUDY RESULTS—BASED ON 11 PATIENTS
IN FISH PEPTIDE GROUP AND 12 PATIENTS IN
PLACEBO GROUP AT THE END OF THE 5-MONTH STUDY

Symptom	Number of Fish peptide patients reporting a decrease in symptom at 5 months	Number of Placebo patients reporting a decrease in symptom at 5 months
Diarrhea	7	2
Nausea	3	1
Constipation	0	0
Bloating	5	1
Fatigue	4	1
MEAN	3.8±2.6*	1.0±0.71

*p=0.0479

REFERENCES

1. Bashir S, Lipman TO. Nutrition in gastroenterology and hepatology. *Primary Care*. 2001;38(3). [PAGE NUMBERS?]
2. Han PD, Burke A, Baldassano RN, et al. Nutrition in inflammatory bowel disease. *Gastroenterology Clinics*. 1999;28(2):423-443.
3. Pfau PR, Rombeau JL. Advances in gastroenterology: *Nutrition. Medical Clinics of North America*. 2000;84(5). [PAGE NUMBERS?]
4. O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of Crohn's disease: A controlled trial. *Br Med J*. 1984;288:1859-1862.
5. Poullain MG, Cezard JP, Roger L, et al. Effect of whey proteins, their oligopeptide hydrolysates and free amino acid mixtures on growth and nitrogen retention in fed and starved rats. *JPEN*. 1989;13:382.

6. Smith JL, Areaga C, Heymsfield SB. Increased ureagenesis and impaired nitrogen use during infusion of a synthetic amino acid formula. *NEJM*. 1982;306:1013.
7. Akobeng AK, Miller V, Stanton J, Elbadri AM, Thomas AG. Double-blind randomized controlled trial of glutamine-enriched polymeric diet in the treatment of active Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2000;30:78-84.
8. Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *NEJM*. 1996;334(24):1557-60.
9. Vernia P, Monteleone G, Grandinetti G, et al. Combined oral sodium butyrate and mesalazine treatment compared to oral mesalazine alone in ulcerative colitis: randomized, double-blind, placebo-controlled pilot study. *Dig Dis Sci*. 2000;45(5):976-981.
10. Roberts PR, Zaloga GP. Dietary bioactive peptides. *New Horizons*. 1994;2(2):237-243.
11. Unno N, Fink MP. Intestinal epithelial hyperpermeability: mechanisms and relevance to disease. *Gastroenterology Clinics*. 1998;27(2):289-307.
12. Bjarnason I, Macpherson A, Hollander D. Intestinal permeability: an overview. *Gastroenterology*. 1995;108:1566-1581.
13. CDC guidelines for preventing opportunistic infections among HIV-infected persons—2002 recommendations of the Infectious Diseases Society of America. *MMWR*. 2002;51(RR-8):1-2.
14. Echeverria PS, Jonnalagadda SS, Hopkins BL, Rosenbloom CA. Perception of quality of life of persons with HIV/AIDS and maintenance of nutritional parameters while on protease inhibitors. *AIDS Patient Care STDs*. 1999;13(7):427-433.
15. Volberding PA, Sande M, Deeks SG. *The Medical Management of AIDS*. Philadelphia, PA: WB Saunders; 1999:97-201.
16. Mooney M, Vergel N. *Built to Survive*. Los Angeles:PoWeR;1999:111-26. [IS THIS A BOOK? IS "PoWeR" THE PUBLISHER?]
17. Chesney M. Adherence to HAART regimens. *AIDS Patient Care STDs*. 2003;17(4):169-177.
18. Kaminski M, Weil S, Bland J, Jan P. AIDS wasting syndrome as an entero-metabolic disorder: the gut hypothesis. *Alt Med Rev*. 1998;3(1):40-53.
19. Oktedalen O, Skar V, Dahl E, Serck-Hanssen A. Changes in small intestinal structure and function in HIV-infected patients with chronic diarrhoea. *Scand J Infect Dis*. 1998;30(5):459-463.
20. van Elburg RM, Uil JJ, Kokke FT, et al. Repeatability of the sugar-absorption test, using lactulose and mannitol, for measuring intestinal permeability for sugars. *J Pediatr Gastroenterol Nutr*. 1995;20(2):184-188.
21. Uil JJ, van Elburg RM, van Overbeek FM, et al. Clinical implications of the sugar absorption test: intestinal permeability test to assess mucosal barrier function. *Scand J Gastroenterol Suppl*. 1997;223:70-8.
19. Bjarnason I, Macpherson A, Hollander D. Intestinal permeability: An overview. *Gastroenterology*. 1995;108:1566-1581.
20. Wyatt J, Oberhuber G, Pangratz S, et al. Increased gastric and intestinal permeability in patients with Crohn's disease. *Am J Gastroenterol*. 1997;92(10):1891-1896.
21. Best WR, Bechtel JM, Singleton JW, Kern F. Development of Crohn's disease activity index: National cooperative Crohn's disease study. *Gastroenterology*. 1976;70:439-444.
22. Hanauer SB, Meyers S. Management of Crohn's disease in adults. *Am J Gastroenterol*. 1997;92(4):559-566.
23. Woodcock A, Bradley C. Validation of the HIV treatment satisfaction questionnaire. *Qual Life Res*. 2001;10(6):517.

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