CellR4 2019; 7: e2746

The use of high-dose Omega-3 PUFAs and Vitamin-D co-supplementation as a therapeutic approach for IBD-related symptoms: case report and literature review

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Keywords: Inflammatory Bowel Disease, IBD, Omega-6 PUFAs, Omega-3 PUFAs, AA/EPA ratio, omega-6/omega-3 ratio, Vitamin D deficiency, Omega-3 supplementation, Vitamin D supplementation, Anti-inflammatory diet.

Abstract

Objective: **Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease characterized by two subtypes, affecting either the colon (ulcerative colitis) or any part of the gastrointestinal tract (Crohn's disease). Although the etiology of IBD remains unclear, nutritional factors such as omega-3 polyunsaturated fatty acids (PUFAs) and vitamin D deficiency have been identified as potential risk factors for IBD development. Omega-3 PUFAs have been under investigation as pharmaconutrients in patients diagnosed with IBD due to their anti-inflammatory effects such as oxidative stress reduction, improvements of mucosal barrier function and intestinal morphology, and reduction of adhesion molecule expression. Further investigation is needed to establish precise recommended daily intake to achieve IBD prevention or sustaining remission, as well as understanding a comprehensive dietary program that may relate to their potential efficacy.**

Case Report: **We report the case of a 22-year old female diagnosed with IBD, who presented with persistent symptoms of lower abdominal pain, bloating, increased bowel frequency, and hematochezia. Further laboratory work up revealed an elevated ratio of arachidonic acid (AA) to eicosapentaenoic acid (EPA) and a vitamin D deficiency. Once she began co-administering high-dose omega-3 fatty acids (6.6 grams of EPA and DHA per day) and high-dose vitamin D (5,000 IU per day), her IBD-associated symptoms significantly ameliorated. Repeat lab work over the course of time correlated these clinical benefits with a significant reduction in her AA/EPA ratio, which serves as a marker of unresolved inflammation.**

Conclusions: **This case report and literature review highlight the potential benefits of co-supplementation of high-dose omega-3 fatty acids and vitamin D as safe and effective therapeutic supplements to treat core symptoms of IBD, especially when coupled with a calorie-restricted anti-inflammatory diet. To investigate the efficacy of this dietary approach, a larger pool of the population must be followed over an extensive period of time, as well as developing a comprehensive theory of the biochemical mechanisms potentially involved in such clinical improvements.**

Introduction

Inflammatory Bowel Disease (IBD), primarily comprised of ulcerative colitis (UC) and Crohn's disease (CD), is a chronic recurrent inflammatory disorder of unknown etiology[1]. Homeostatic imbalance between the gut mucosa and the intestinal immune system, as well as environmental factors, suggest complex intersections in disease development[2]. Pathophysiology of IBD begins with compromised gut barriers allowing increased entry of microbial fragments to interact with toll-like receptors (TLR) on the surface of epithelial and immune

cells in the intestine[3]. This results in the activation of pro-inflammatory gene transcription factor, nuclear factor kappa B (NF-κB). Activation of NF-κB leads to increased generation of pro-inflammatory cytokines production, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, -6, -12, and -23[4]. Because of increased gut permeability, antigens that would be normally prevented from interacting with the epithelial and immune cells in the intestine can now be presented to CD4-T cells and natural killer cells which produce IL-13, found to be associated with weakening of the epithelial cell barrier caused by the breakdown of epithelial tight junctions resulting in further increased intestinal permeability[5]. Chronic inflammation experienced by IBD patients induces bowel pain, bleeding, as well as increased risk for bowel cancer. Also, due to IBDs recurrence and prolongation, quality of life of the patient is heavily impacted[4]. The high cost this chronic disease places, as well as its severe impacts on quality of life, has emphasized the importance of finding potential biomarkers associated with disease onset and using new alternative approaches to disease management by changing those biomarkers.

Although there may be genetic predisposition associated with the development of IBD, environmental factors, such as diet, have been found to play a major role in disease occurrence. Epidemiological studies reveal increased incidences of IBD, with highest annual cases reported in Europe and North America [6]. Over time, changes in dietary habits have resulted in an increased ratio of n-6/n-3 polyunsaturated fatty acids (PUFAs), especially in the Western diet composed of higher consumptions of processed red meats, high-fat dairy, refined grains, vegetable oils, and highly sweetened beverages[7,8]. Of particular interest are the increasing incidences of IBD in Japan and Eastern Europe, where IBD was once uncommon[9,10]. Previously these diverse regions had diets richer in vegetables, fruits, and fish[8]. Increasingly westernized food consumption has resulted in increasing diet-induced inflammation. One indication of this increased inflammation has been a significant rise in omega-6/omega-3 ratio to greater than 15, thereby resulting in increased pathogenesis of certain diseases associated with increased inflammation such as obesity, diabetes, cardiovascular disease, autoimmune diseases, and cancer[11]. Data from epidemiological studies report families who relocated from regions having a low IBD incidence to regions with higher IBD incidences demonstrate their children have the same risk of IBD development as children whose families resided in the higher IBD-incidence regions[12]. This has led researchers to suspect westernization of diets as a possible IBD etiologic factor[10].

Specifically, increased consumption of pro-inflammatory n-6 PUFAs, such as linoleic acid (LA) and arachidonic acid (AA), have been specifically associated with increased incidences of IBD[13]. Overall, repeated studies have identified patterns wherein genetically modified mice expressing colitis consistently following a diet rich in omega-6 fatty acids experienced increased inflammatory symptoms of the colon or small intestine, as well as associated mucosal barrier dysfunction[14,15]. Pathogenesis of IBD reveals the impact of oxidative stress and the production of prostaglandin (PG) through COX pathway on mucosal integrity, resulting in chronic low-level inflammation. Classic cyclooxygenase (COX) inhibitors such as non-steroidal anti-inflammatory drugs (NSAIDs) are used to block PG biosynthesis[16]. This approach is being replaced by monoclonal antibodies that bind to tumor necrosis factor to reduce inflammation[9]. However, these pharmacological interventions often have unwanted side effects, which result in limited long-term use. As a consequence, anti-inflammatory nutrients may play a potential role in clinical care of IBD patients, such as constructing the intestinal microbiome and modifying inflammatory responses. Growing research has focused on the use of nutritional approaches to maintain remission and prevent disease progression[9]. Likewise, there is a growing emphasis placed on anti-inflammatory diets used to naturally treat IBD, involving the reduction of pro-inflammatory food consumption and an increased variety of food categories promoting favorable gut microbiome[10]. Recent data has emphasized the potential benefits of omega-3 PUFAs in UC therapy, where a higher consumption of omega-3 PUFAs may lower the incidence of disease[17].

Omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been widely investigated for their anti-inflammatory properties and in treatment of chronic inflammatory diseases such as IBD, but what the required levels are for a therapeutic dose remain unknown. Although EPA and

DHA synthesis occurs through numerous elongation and desaturation steps using α-linolenic acid (ALA; 18:3 n−3), this synthesis route is slow and inefficient in humans. To reach a potential therapeutic dose of EPA and DHA, humans must consume omega-3 PUFAs through dietary intakes of sources of pre-formed EPA and DHA, such as fatty fish or supplementation with EPA and DHA concentrates[4,5]. Potential anti-inflammatory benefits of omega-3 PUFAs result from the competition in the pro-inflammatory pathways involving cyclooxygenase or lipoxygenase enzymes. EPA competes with arachidonic acid (AA), a n-6 PUFA for binding site in COX enzymes, thus inhibiting AA conversion to pro-inflammatory eicosanoids, such as prostaglandins and leukotrienes[4]. This competitive pathway was demonstrated by parenteral delivery of various oils containing different ratios of omega-3 and omega-6 fatty for 3 days, then inducing intestinal ischemia for 100 minutes to examine intestinal damage determined by histological damage assessment. The intestinal tissue damage was found to be significantly reduced in the fish oil group (rich in EPA and DHA), compared to that of the soybean oil group containing omega-6 fatty acids[18]. Furthermore, omega-3 PUFAs can be synthesized into a group of newly discovered hormones (specialized pro-resolving mediators) that are critical in the resolution of existing inflammation[8,19,20].

In relation to pain management, the effects of omega-3 PUFAs on IBD-related symptoms depend on the intake value and cellular distribution. Pain relief has been linked to omega-3 PUFAs by either decreasing the intensity of the inflammatory response or increasing the resolution of existing inflammation, or by inhibition of mitogen-activated protein kinase activity that interprets sensitization and neuropathic pain. The role of EPA and DHA in pain regulation has been associated with their anti-inflammatory and pro-resolution effects, as well as indirectly releasing opioid peptide β-endorphins[2]. Investigators have concluded the likelihood of flare inductions are commonly related to the consumption of increased quantities of primarily red and processed meats[21]. Likewise, the administration of iron, the main component found in red meat, has been found to negate the positive effects of these anti-inflammatory regimens[22]. Studies have also demonstrated the negative outcomes of oral administration of iron sulfate or heme, both commonly found in meat, concluding these components intensifies chemically induced colitis in mice and rats[23]. Other indications of dietary influences include increased omega-6/omega-3 ratios were associated with increased likelihood of symptom relapse patients with CD[24].

Finally, children with IBD also have increased prevalence of vitamin D deficiency that may promote imbalances between calcium and immune homeostasis, as well as interfere with T-cell development. This would lead to increased susceptibility to autoimmune diseases such as IBD, as well as decreasing bone health[25-27]. Hypovitaminosis D in patients with IBD has also been suggested to arise from factors such as decreased sunlight exposure, reduced food consumption of vitamin D, and mal-absorbed nutrition[28]. Vitamin D supplementation appears to reduce IBD-associated inflammation potentially involving increases in anti-inflammatory cytokines like IL-10 along with the suppression of pro-inflammatory IL-6 and IL-17 pathways[29].Vitamin D supplementation also decreases intestinal permeability, increases protection against TNF- α -induced injury, as well as molding favorable intestinal microbiota[30]. Sufficient evidence has demonstrated the activation of T-cells promoting IBD through exaggerated immune response to antigens located in the gut, such as Th-1, Th-2, and Th-17[31]. Recent studies have revealed vitamin D receptor, 1,25 $(OH)_2D_3$, has been found to regulate immune responses through the stimulation of T-cell activity and the inhibition of Th-1 and Th-17 cell proliferation[25].

With this background of what is known about potential dietary inputs to IBD, the purpose of this case report is to provide new potential therapeutic intervention using a combination of high-dose ultra-refined omega-3 fatty acid and vitamin D3 in the context of an anti-inflammatory diet. We describe the case of a 22-year old young adult female with ulcerative colitis diagnosed in 2014. She presented with worsening bowel changes, which gradually improved throughout consistent co-supplementation of high-dose omega-3 fatty acids and vitamin D, while following an increasing strict anti-inflammatory diet. Throughout this case report, we provide a literature review demonstrating the efficacy and potential benefits of nutritional approaches for the treatment of IBD-related symptoms.

Materials and Methods

Whole blood fingerstick testing was used to determine the AA/EPA ratios as a marker of systemic inflammation. Dietary compliance was determined using a Food Log. Changes in IBD-associated symptoms were done using Daily Journal (Symptom Tracker) and an overall IBD score were generated using My IBD Manager from the American Gastroenterological Association. An ultra-refined liquid EPA and DHA concentrate (75% EPA and DHA) was obtained from Zone Labs, Inc.

Case Presentation

L.B., a 22-year old female presented with constant lower abdominal pain, bloating/distention, gas, weight gain, altered bowel habits resulting in diarrhea and constipation, increased bowel frequency, hematochezia, and dehydration. She underwent an esophagogastroduodenoscopy and colonoscopy with biopsies on 2/26/14, pathology revealed chronic gastritis in the duodenum and stomach, as well as moderate to severe active colitis of the descending colon, with mild architectural irregularity. There was also chronic active proctitis with ulceration in the rectum with no granulomas or dysplasia present. Steiner stains were negative for *Helicobacter pylori*-like organisms. Overall, the findings were suggestive of inflammatory bowel disease.

She began taking the anti-inflammatory drug mesalamine 400 mg tablets (bi-daily) and ferrous sulfate 325 mg daily with breakfast. She also followed a low Fermentable Oligo-, Di-, Mono-saccharides And Polyols (FODMAP) diet, modifying daily oral intake to five small-frequent meals, and avoided highly processed foods. The low FODMAP emphasized a plant-based whole food diet, with low saturated fats (and no fried foods), as well as a moderate intake of meats. Each of the patient's meals included a source of protein (opting for organic or grass-fed protein), followed by chicken cooked without skin. Oral intake of fish was around at least twice per week, while red meats consumptions were limited in her diet to around 1-2 times per week.

In order to treat constipation, the patient used Senna tablets (17 mg/day) at night, restricting intake to no more than 34 grams/day. For abdominal pain management, the patient used IBgard peppermint oil enteric-coated capsules. She also consistently took liquid multivitamin daily. Finally, to regulate symptoms such as gas and bloating, she took Iberogast with every meal.

Increasing her intake of the anti-inflammatory drug (4.8 g daily) slightly improved her symptoms around 8 weeks of consumption. She experienced reduced bowel movements to 1-2 times per day and without bleeding; therefore, she was instructed to diminish her dose to around 2 pills a day. Only as needed for breakthrough bleedings, the patient would take Canasa suppositories. The patient also began taking probiotics daily; the starting dose was 30 Billion, as well as 300 mg of EPA and DHA per day as a omega-3 fatty acid supplement. At least 150 minutes of physical activity per week was emphasized to maintain a regular and healthy lifestyle.

Following these dietary, supplement, and lifestyle changes the patient underwent a repeat screening colonoscopy with biopsies on 11/20/15, pathology revealed left-sided ulcerative colitis without complications with erythema and friability present in the 0-30 cm biopsy. There appeared to be very mild active colitis in the transverse colon, as well as active chronic granulomatous colitis of moderate severity consistent with Crohn's disease in the left colon. Active chronic colitis consistent with inflammatory bowel disease and suggestive of Crohn's disease in the colon biopsy at 30 cm.

Initial inflammatory screening using a fingerstick blood test evaluated on 05/17/2016, revealed an AA:EPA ratio of 19, which was significantly higher than the desired target ratio of 1.5 to 3. Furthermore, her EPA level was 0.5% of total fatty acids, which was low compared to the EPA target range of > 4% of total fatty acids. The patient began with starting dose of an ultra-refined omega-3 fatty acid concentrate containing 6.6 grams of EPA and DHA per day, which was 20 times greater than her previous EPA and DHA intake.

As of 06/02/2016, the patient began increasing her intake of EPA and DHA and started an intake of vitamin D beginning with a daily oral intake of vitamin-D (25-OH Cholecalciferol) supplementation of 5,000 IU per day. The intake of EPA and DHA continually was adjusted through routine inflammatory screenings evaluating AA/EPA ratios to achieve a target goal between 1.5-3.0. The patient also began following a more strict anti-inflammatory diet based on calorie restriction (1,200-1,500 calories per day), yet maintaining a diet that incorporated adequate protein, moderate in low-glycemic

carbohydrate (primarily non-starchy vegetables), and low total fat (but rich in monounsaturated fat), and also rich in fermentable fiber. This type of calorie-restricted, anti-inflammatory diet is commonly referred to as the Zone Diet.

The patient re-evaluated inflammatory levels on 02/06/2017, which reported AA levels at 12.1% and EPA levels around 2.1%, with an overall AA/EPA ratio of 5.8. The patient now completely eliminated poultry and red meat from the Zone Diet and used fish as an animal source of protein to lower the AA levels. She re-tested on 11/28/2017, which revealed an overall AA/EPA ratio of 4.8 with AA levels around 8.6% and EPA levels at 1.8%.

Continuing on a strict pescatarian Zone Diet, with vitamin D, and increased omega-3 supplementation, the patient re-evaluated her fatty acid profile on 03/06/2018, reporting an overall AA/EPA ratio of 2.8, within the ideal target range of 1.5-3.0. Final re-evaluation on 04/21/2019 revealed stable targeted AA/EPA ratio of 2.8, with AA slightly decreasing to 8.6% now within a goal range of 7-9%, and her EPA levels had increased to 3.4%.

With the use of a fish-based Zone Diet, coupled with high-dose supplementation of ultra-refined 10g EPA and DHA supplement and daily supplementation with high-dose vitamin-D 5,000 IU (25-OH Cholecalciferol), the patient reported a significant amelioration in her IBD symptoms, including frequent bowel movements, appearance of bloody stools, lack of abdominal pain, constipation, dehydration, bloating, diarrhea or increased gas. She has experienced significant weight loss, yet she reports increased appetite and continues participating in regular daily activities and exercise.

Conclusions

IBD places a large burden on the quality of life of patients and a high cost for public health management. The use of omega-3 PUFAs, such as EPA and DHA, are seen as both safe and natural supplements in minimizing and preventing inflammatory processes associated with diseases such as IBD. Omega-3 PUFAs have been found to improve patient quality of life through balancing blood lipid levels, membrane fluidity, resulting in decreased fatigue, as well as improving peripheral neuromuscular and brain function. Due to inflammatory nature of IBD, high-dose omega-3 PUFAs using ultra-refined supplements in conjugation with high-dose vitamin D and a strict anti-inflammatory diet may be helpful in IBD treatments, alleviating symptoms and recovering induced mucosal barrier dysfunction. It is our speculation that all of these dietary interventions may result in the activation of AMPK, the gene-transcription factor that is the master genetic switch for metabolism and ultimate repair of damaged tissue[33,34].

Further research is required to fully understand the hormonal and genetic influences of the combination of omega-3 PUFAs, vitamin D, and anti-inflammatory diets on IBD. Further studies will also be beneficial in establishing a recommended daily guideline to treat, and induce long-term remission, if not reversal, of IBD.

Disclosures:

Barry Sears is the president of a medical food company that donated the ultra-refined omega-3 concentrate used in this study. Luciarita Boccuzzi declares no conflict of interests.

Informed Consent:

The participant in this study signed the informed consent.

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