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Role of Omega-3 Fatty Acids in Irritable Bowel Syndrome (IBS)

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Abstract
Background: Dietary supplementation with Omega-3 (ω-3) fatty acids (FAs) has been demonstrated to elicit several effects ranging from decrease in blood pressure, anti-arrhythmic effect and decrease in inflammation in inflammatory bowel disease, asthma and rheumatoid arthritis. Irritable bowel syndrome (IBS) is a chronic disorder characterized by abdominal pain and irregular bowel habit. It is associated with visceral hypersensitivity, increased mucosal permeability and a low-grade mucosal inflammation. Commercially available omega (ω)-3 polyunsaturated fatty acids (PUFA) are being prescribed as empirical treatment for many chronic ailments including IBS.
Aim: To examine literature available support use of ω-3 PUFA in IBS.
Methods: We conducted a search using "Omega 3 fatty acids supplementation" on the PubMed, Scopus, and databases (e.g. Medline, Cinahl, Embase, and Science Citation Index Expanded) from 1966 to December, 2015.
Result: The gut microbiota in IBS is associated with an imbalance of Firmicutes/ Bacteroidetes ratio. This imbalance has an impact on gas and metabolite production such as short chain fatty acids. Omega-3 FAs are anti-inflammatory, while ω-6 FAs are proinflammatory.
Conclusion: The benefit of ω-3 FAs for IBS requires more clarification by prospective studies. Current claims of long chain PUFA supplementation in IBS should be viewed with caution.
Keywords: irritable bowel; omega-3 fatty acids; anti-inflammatory; omega-6 fatty acids; proinflammatory

1. Introduction

Polyunsaturated fatty acids, referred to as "Essential fatty acids" (EFAs) for animals and humans, are present in the diet. These EFAs include Linoleic acid (omega-6 fatty acid) and alpha-linolenic acid (omega-3 fatty acid). Dietary EFAs are sub-classified as omega-6 (ω-6) or omega-3 (ω-3) fatty acids (FAs) on the basis of omega end first double bond location in their carbon chains [1]. Linoleic acid is a ω-6 fatty acid and alpha-linolenic acid (ALA) is a ω-3 fatty acid. These FAs lead to eicosanoic acids formation ending up in generation of prostaglandins, lipoxins, leukotrienes and thromboxanes. Essential fatty acids are converted into harmful trans-fatty acids during hydrogenation. The main ω-3 FAs include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and ALA. ALA is the most common ω-3 FAs in all Western diets. It is found in vegetable oils, leafy vegetables, and in some animal fat. The human body uses ALA for energy, while conversion into EPA and DHA occurs in the liver is on a small scale.

The ancient populations consumed equal amounts of ω-6 and ω-3 FAs and less saturated fat, than the present-day affluent developed world [2-3]. In the developed countries diet is high in ω-6 FAs with ratio of ω-6 FAs to ω-3 FAs being 20–30:1. There is decreased fish consumption in these populations [4]. High amounts of ω-6 FAs increases concentrations of arachidonic acid (AA) metabolic products, specifically hydroxy fatty acids, leukotrienes, prostaglandins and thromboxanes. These contribute to excessive cell proliferation, allergies, inflammatory disorders, atherosclerosis and thrombosis in blood vessels [4]. These side effects of ω-6 FAs are counteracted by ω-3 FAs by increasing the concentrations of prostaglandin I_3 and decreasing thromboxane A2, and prostaglandin E2[4]. In addition, ω-3 FAs suppress interleukin (IL) 1β, IL-6 and tumor necrosis factor α (TNF-α) [5]. The aim of this review was to determine the potential benefits and role if any of ω-3 FAs treatment in patients with IBS.

2. Literature Review

We conducted a search using "Omega 3 fatty acids supplementation" on the PubMed, Scopus, and databases (e.g. MEDLINE, CINAHL, EMBASE, and Science Citation Index Expanded) from 1966 to December, 2015. The reviewers independently screened all full-text publications and abstracts. The details abstracted from publications included study

design, sample size, patient population, country, etc. We also checked the bibliographic references of textbooks and reviews and editorials. Eligible studies were published in English, conducted in different world populations and considered ω-3 FAs for treatment of IBS.

2.1 Benefits of Omega-3 fatty acids

Omega-6 FAs are proinflammatory contained in vegetable oils and meat while ω-3 FAs have potential health benefits. Dietary supplementation with ω-3 FAs has been demonstrated to elicit effects ranging from a decrease in blood pressure, anti-arrhythmic, anti-thrombotic, and is also known to decrease inflammation in inflammatory bowel disease, asthma and rheumatoid arthritis. Increased consumption of cooking oils high in ω-6 FAs has increased the ratio of ω-6 to ω-3 FAs from 1:1 in the early diet of the human to 10:1. The biological role of ω-3 FAs contributed to a low rate of coronary heart disease (CHD) in Japanese as well as in Greenland populations [6-7]. Fish regularly consumed by these populations is rich in ω-3 FAs. A high fish intake was associated with a low risk of mortality from CHD in studies originating from Netherlands [8], Sweden [9] and USA [10]. The benefits of dietary consumption of ω-3 FAs have been demonstrated in CHD [11-12], dyslipidemia [13], atherosclerosis [14], hypertension [15], metabolic disorders [16-17], vascular reactivity [18], obesity [19], inflammatory diseases [20-21] neurological/ neuropsychiatric disorders [22], renal pathologies [23], osteoporosis [24], eye diseases[25] and pregnancy[26]. Current recommendation is to have a low ω-6: ω-3 ratio and an increased amount of dietary ω-3 FAs [27-28]. When this ratio was reduced, it improved the lipid profiles in the age group of 45–70 years in United Kingdom diet study. It did not influence lipase activity, insulin sensitivity, and hemostasis risk factors [29-30]. Omega-6 FAs proinflammatory effect is attributed to its metabolites [2]. The membrane phospholipids of the blood inflammatory cells have abundant AA compared to the ω-3 EPA and DHA [3-6]. The ω-6 FAs shift plays a role in several diseases including IBS [7-8]. Globally, there is more stress on disease prevention, and ω-3 FAs is of interest for healthcare practitioners worldwide.

2.2 Omega-3 fatty acids in gastrointestinal disorders

Omega-3 FAs dietary supplementation reduced disease activity in active ulcerative colitis and there was an increase in weight [31]. However, a meta-analysis did not find ω-3 FAs maintaining a remission [32]. In contrast, another study in Crohn's disease patients found ω-3 FAs in enteric-coated capsules safe and effective for maintaining remission [33]. A large randomized study did not show any benefit [34]. In a cohort study involving fish consumption as a dietary source of ω-3 FAs reduced colorectal cancer risk [35]. Subjects with celiac disease (CD) after 1 year of remission were shown to have low levels of PUFA [36], so dietary ω-3 FAs supplements may be of help.

2.2.1 Irritable bowel syndrome

IBS is a functional symptom complex present in 10% of the world population and is characterized by abdominal pain or bloating associated with altered bowel movement in the absence of morphological and histological changes [37]. It represents a complex interplay of several factors including gut microbiota and low-grade inflammation [38]. A modification of the gut microbiota is present in IBS patients with an imbalance of *Firmicutes*/*Bacteroidetes* ratio [39]. In an individual patient, these factors interact to generate symptoms with an increase in mucosal permeability and a low-grade inflammation of the colonic mucosa [40-41]. In IBS, an imbalance of cytokines is observed with proinflammatory TNF-α exceeding anti-inflammatory IL-10[42]. This was significantly demonstrated in female IBS patients compared to controls [42].

Patients with IBS often adopt variety of dietary precautions to reduce their symptoms, which usually have no scientific basis. Having said that, IBS symptoms may be caused or exacerbated by dietary components and a diet that is restricted in fermentable, and poorly absorbed carbohydrates is beneficial [43]. Insoluble fiber may aggravate symptoms. An increased intake of soluble fiber improves symptoms of IBS constipation subtype. Prebiotic fibers found in fruits, vegetables e.g., onions and garlic have not been adequately tested. The usefulness of probiotics such as live-culture yogurt is not recognized. In clinical practice, it is difficult to ascertain that a patient's symptoms are related to diet. Several methods are often used including a modified exclusion diet or stepwise reintroduction of foods. There is a recent trend to design diet for IBS that has low content of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs). Since their ingestion is associated with intestinal distention and excess gas production, their reduction in diet may improve functional gastrointestinal symptoms.

2.3 Effect of ω-3 FAs on prostaglandin and cytokine production

Clarke, et al hypothesized that inflammation in IBS was due to the increase in ω-6 compared to ω-3 FAs that resulted in increased AA derived active metabolites [44]. They measured plasma PUFA profile and analyzed total plasma content of ω-6, ω-3, and their ratio, AA, PGE2 and Leukotriene B4 (LTB4).They found altered circulating AA and their metabolites were significantly elevated in all IBS subgroups [45]. Another study related possible gender differences in PUFA profiles to sex hormones [46]. The increase in AA in mild, moderate, or severe IBS was non-significant. There was no association between FAs levels and IBS symptoms. The elevated AA levels in IBS cohort were associated with significant elevations of PGE2 and Leukotriene B4 (LTB4). LTB4 is involved in inflammation, as it is a potent neutrophil

chemoattractant leading to reactive oxygen species formation and liberation of lysosomal enzymes [47]. Serum PGE2 concentrations were elevated in the diarrhoea dominant-IBS subtype, whereas LTB4 levels were equally increased in all IBS subtypes. The source of elevated IL-6 levels in IBS has not been identified [48-49]. PGE2 is known to cause elevation of IL-6 levels by activating COX-2 enzyme [50-51]. The altered biological cascade may lead to the abnormal basal IL-6 profile in IBS following long standing high PGE2 level [44]. However, PGE2 level did not have an antiinflammatory effect on IL-6[52]. PUFA derived AA metabolites also have functional consequence on intestinal barrier function [53]. Elevated PGE2 levels may have a role in altered GIT motility [54]. As circulating PGE2 crosses the blood brain barrier, the brain-gut axis and the enteric nervous system can be affected [55]. In IBS, an increase in number of immune cells in the gut indicates immune activation [56-57]. LTB4 activated morphological and functional changes in the mast cells and also acted as a chemoattractant for their progenitors in IBS [58-60]. Changes in prostaglandin levels may impact the brain-gut axis via their effect on hypothalamic-pituitary-adrenal-axis secretory activity [55]. These could influence several aspects including motility, secretion, nociception, cytoprotection, etc., of the gastrointestinal tract [61-62]. Arachidonic acid and its metabolites may also contribute to the IBS associated physiological changes and symptomatology. Clark et al described increases in the AA levels with a shift toward the ω-3 PUFA. This change is difficult to explain and do not agree with other disorders with elevated immune parameters [63-64].

2.4 Dietary PUFA

In a previous study, an increased ratio of ω-6: ω-3 was associated with particular cytokine genotypes [65]. However, dietary habits of IBS cohort was not considered, hence these changes could be attributed to the dietary restriction in consumption of fatty acids. These dietary alterations would have an anti-inflammatory outcome [65]. IBS is not less common in Japan and other countries with high fish consumption compared to in Western countries [66]. This suggests that dietary factors alone were insufficient to counteract the input of the AA metabolic pathways. The phospholipase A2 (PLA2) released AA from the cell membranes and its activity also need further investigation [67]. Mead acid, an indicator of essential fatty acids (EFA) deficiency, is often increased when there is a decrease in the EFA 68. The proportions of Mead acid were not increased in IBS vs control indicating a normal level of linoleic and alpha-linolenic EFA [69].

2.5 Gender

As described before, in female IBS patients the PUFA profile shows increased AA levels in the clinical setting [44]. Gender differences in PUFA profiles may exist [44,45,69]. Any gender differences in PUFA profile may be related to sex hormones. However, in none of these studies dietary habit of the subjects with IBS was presented that could be responsible for alterations in pro-inflammatory markers [46]. The IL-6 may represent a biomarker of IBS that should be compared to the current symptom-based diagnostic scheme.

2.6 PUFA for the treatment of IBS

Several symptomatic treatment regimens attempt to relieve symptoms, using dietary soluble fiber, psychotherapy and medications targeting various symptoms. One should also consider including PUFA. In IBS, the relative deficiency in PUFA promote saturated and monounsaturated fatty acids that makes a case of dietary PUFA supplementation [70].

2.7 Impaired EFA metabolism

Poor dietary intake, malabsorption and impaired EFA metabolism could lead to deficiency of PUFA. These are derivatives of long chain polyunsaturated fatty acids (LCPUFA) [71-72]. In IBS subjects decrease in both AA/linoleic acid and docosahexaenoic acid/alpha-linolenic acid ratios reflected their reduced biosynthesis and may be due to intestinal malabsorption of PUFA [73]. EFA deficiency is not uncommonly seen in malabsorption, catabolic illness, etc.[74].

3. Animal studies

There is no evidence that ω-3 FAs treatment has any efficacy in IBS treatment. In animal model of post stress visceral hypersensitivity associated with mast cell activation was not reversed by LCPUFA [75]. ω-3 FAs activated nuclear peroxisome proliferator-activated receptor g (PPARG). This negatively regulated inflammatory cytokine production via interference with transcription factors activation [76]. The PPARG agonists reduced the production and release of histamine by mast cells [77-78]. The reversal of post stress visceral hypersensitivity has also been demonstrated with histamine-1 receptor antagonists (Ebastine)[79].There are previous animal experimentation and clinical trial that studied the mast cell stabilizer (Ketotifen, Doxantrazole) use in IBS [79-81]. LCPUFAs modulated mast cell mediator release [82-84]. Doxantrazole [85] and Ebastine [80] successfully reversed post-stress visceral hypersensitivity in animal model. However, it was not achieved with ω-3 FAs treatment. Celinski et al [86] showed rosiglitazone suppressed inflammatory response and proinflammatory cytokines in dextran sodium sulphate colitis. Some reported inhibition of mast cell release of cytokines and inflammatory mediators [83-84, 87] while others report augmentation [88-89].

4. Conclusion

Omega-3 fatty acids are required in the diet for healthy nutritional state. It is important to exclude EFA malabsorption when treating IBS. The therapeutic of ω-3 FAs use in IBS demands more investigation and clarification. Any claims of ω-3 FAs efficacy in IBS should be regarded with caution.

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