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## A Study of Comorbidities and Nutritional Supplements Strongly Associated with Inflammatory Bowel Disease

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## **Abstract**

Inflammatory bowel diseases (IBD) are a group of chronic conditions of the gastrointestinal (GI) tract. Crohn's disease and ulcerative colitis are two primary types of IBD. Some pathologic ramifications of these diseases include weight loss, diarrhea, anemia, osteoporosis, and malignancies. The purpose of this study was to find potential unestablished associations between comorbidities linked to an inflammatory state, nutritional supplements used to help alleviate inflammation and promote wellbeing, and the psychological toll on patients.

A deidentified database of 404 IBD patients built by Binghamton Gastroenterology Associates collected information on demographics, medical treatment, symptoms, and medical problems, including psychological disorders. We used semantic connectivity maps obtained through the Auto-Connectivity Map (CM) system to visualize relationships in our data. We aimed to identify possible associations between nutritional supplements (vitamin D, multivitamins, omega-3, and folic acid) and inflammation related to arthritis, cardiovascular disease, and hypertension, along with correlations to anxiety and depression. Our results reflect a close association between arthritis and hypertension (LS=0.68). Folic acid is linked to anxiety (LS= 0.74) and CVD (LS= 0.73). A strong association exists between lack of omega-3 intake and both arthritis (LS= 0.85) and depression (LS= 0.85). Depression and vitamin D intake are also associated (LS= 0.80). The association between arthritis, hypertension and CVD could be a direction for future research.

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## **Introduction**

Inflammatory bowel diseases (IBD) are a group of chronic conditions of the gastrointestinal tract. Crohn's disease and ulcerative colitis are the two primary types of IBD. Crohn's disease is characterized by inflammation in any part of the digestive tract, while ulcerative colitis generally appears in the colon and rectum (MFMER, 2015).

Some of the pathologic ramifications of these diseases include weight loss, diarrhea, anemia, osteoporosis, and malignancies (CCFA, 2015). The purpose of this study was to find potential unestablished associations between comorbidities linked to an inflammatory state, nutritional supplements used to help alleviate this inflammation and promote wellbeing, and the psychological toll on patients.

It is believed that the autoimmune response seen in inflammatory bowel diseases leads to a systemic inflammatory response and may account for the associated joint pain many patients experience (CCFA, 2015). In addition, this systemic inflammatory response could affect other

organs like the heart and the brain. People with arthritis and IBD experience discomfort, stiffness, decrease in flexibility, and edema in the joints that are inflamed. Frequently, joint symptoms parallel IBD symptoms; joint inflammation and swelling worsen when GI symptoms are exacerbated (Harvard Health, 2014). According to the Crohn's and Colitis Foundation of America (CCFA, 2012), between ten and twenty percent of individuals with IBD experience joint pain. Treatment of GI tract disorders tends to alleviate associated joint pain.

Although dietary choices do not seem to cause or contribute to IBD, once a patient is diagnosed with these disorders, improving one's diet can decrease symptoms and the risk of flare-ups. Individuals with IBD have an increased risk of becoming malnourished due to loss of intestinal villi, the major absorptive site in the GI tract. Malabsorption of proteins, fats, carbohydrates, water, and many important vitamins and minerals is mostly affected (CCFA, 2015). In addition, associated symptoms such as nausea and abdominal pain result in decreased appetite and subsequent weight loss.

Several nutritional supplements typically recommended by gastroenterologists are vitamin D, omega-3 fatty acids, and folic acid. Vitamin D regulates many functions of the immune system. Since the 1980's, vitamin D deficiency has been considered a risk factor for IBD. In fact, a deletion in the vitamin D receptor gene in animal models is associated with more severe IBD (Ardesia, 2015). Therefore, individuals with low levels of vitamin D are at a higher risk of developing IBD. Omega-3 fatty acids reduce inflammation by targeting cyclooxygenase 2 (COX2), a molecule which contributes to the synthesis of pro-inflammatory prostaglandin molecules. According to Artemis P. Simopoulos (2002), the founder and president of the Center for Genetics, Nutrition and Health, several clinical trials show that omega-3 fatty acids provide anti-inflammatory benefits in autoimmune and inflammatory diseases, such as cardiovascular disease, arthritis, major

depression, and IBD. In addition, patients with IBD often have low serum levels of folic acid (Burr, 2016). Folate is a methyl donor in the one-carbon metabolic pathway involved in DNA synthesis and the regulation of gene function. Therefore, deficiency of folate may disrupt many physiological functions and increase risk for chronic diseases, including cancer. One concern with folate deficiency is elevated serum levels of homocysteine, a toxic amino acid that increases inflammation. In fact, ulcerative colitis increases the risk of developing colorectal cancer, and supplementation of folic acid reduces the risk (Burr, 2016). Folic acid supplementation decreases serum levels of homocysteine, thereby reducing inflammation. Inflammation increases the risk of many comorbidities such as CVD, hypertension, cancer, anxiety, among others.

Mounting evidence in the literature suggests that patients with IBD commonly exhibit anxiety and depression, and that these psychological conditions tend to worsen during periods of flare-ups (Graff, 2009). Quality of life is highly impacted, especially when the gastrointestinal symptoms are poorly controlled. In fact, patients with IBD and other inflammatory bowel disorders experience rates of depression triple that of the general population (Fuller-Thomson, 2006). Certain immunological biomarkers representative in inflammatory conditions are also seen in patients exhibiting depression and anxiety (Miller and Raison, 2016). It has become evident that a proinflammatory state affects virtually all organ systems and requires a multidimensional treatment approach.

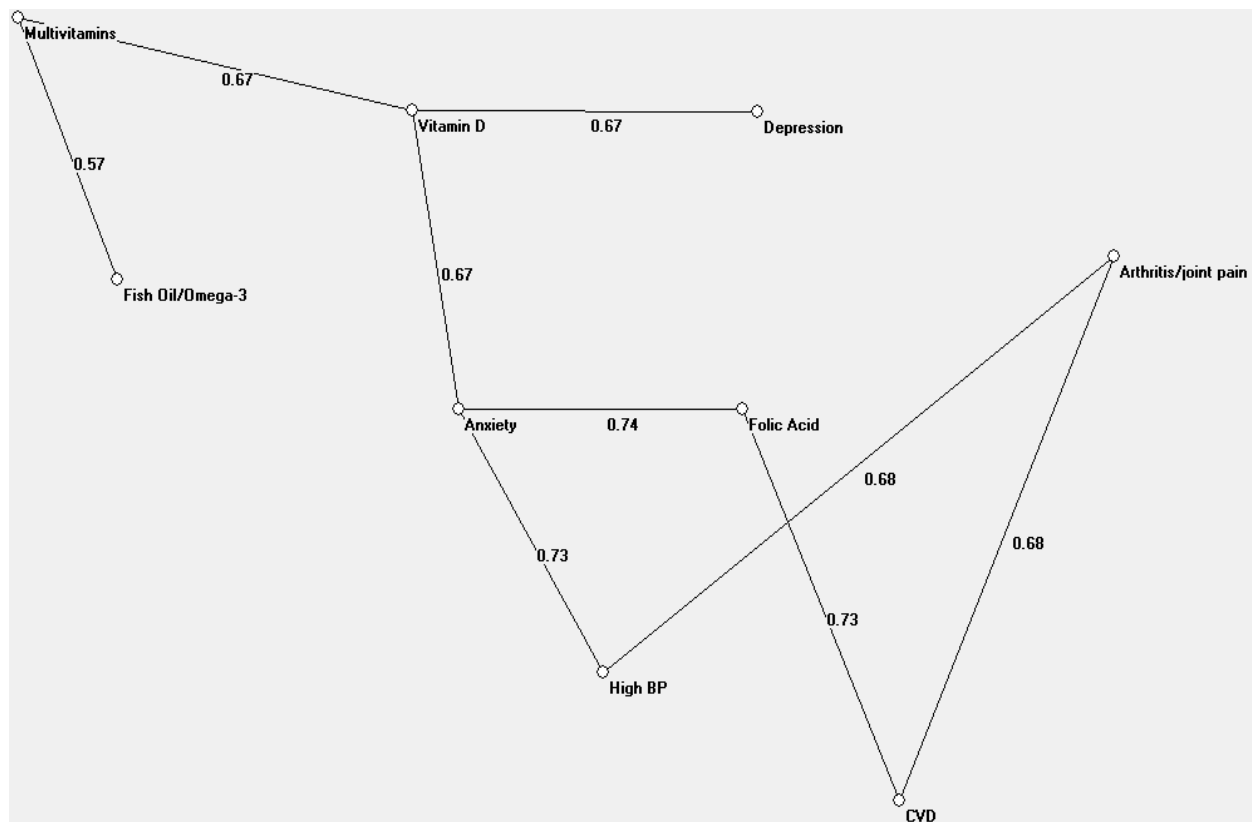
## **Methods**

A database of 404 IBD patients from Binghamton Gastroenterology Associates in Binghamton, NY was created between August 2015 and October 2016. This database collected information on demographics, medical treatment, intestinal and non-intestinal related symptoms,

and other medical problems, including psychological disorders. No identifiers were included in the database. A semantic connectivity map (CM) obtained through the Auto-CM system, a fourth generation artificial neural network (ANN), was created to identify possible associations between nutritional supplements (vitamin D, multivitamins, omega-3 fish oil, and folic acid) and inflammation-related diseases such as arthritis (all types), cardiovascular disease, and hypertension (primary/secondary), and documented anxiety and depression. The Auto-CM is a highly sensitive statistical method capable of identifying different associations between multiple variables through generation of a numerical link strength value (LS). LS values range between zero (no association) and one (the strongest association). The LS value is a marker of the association of strength. For example, an LS value of 1, 0.70-0.5, and 0 would indicate a very strong, moderate or no association between the two variables, respectively.

## **Results**

The two Auto-Connectivity maps (Figures 1 & 2) represent the link strength between different variables. The variables are plotted and connected with a line, and the associated LS value appears on the line. As depicted in Figure 1, the Auto-CM system showed a moderate association (LS=0.68) between arthritis/joint pain and high blood pressure in IBD patients. It also indicated a stronger association between folic acid and both CVD (LS=0.73) and anxiety (LS=0.74), as well as between anxiety and high blood pressure (LS= 0.73).



**Figure 1.** An Auto-Connectivity Map (Auto-CM) showing general associations. Figure 2 indicates that a strong association exists between no omega-3 intake and both arthritis/joint pain (LS=0.85) and depression (LS=0.85). It also suggests that depression is associated with vitamin D intake (LS=0.80) and with anxiety (LS=0.85).



eighteen-month folic acid treatment greatly reduces arterial plaque thickness. In the same study, homocysteine levels were also significantly decreased in patients who received folic acid treatment.

As for the association between arthritis and hypertension, oxidative stress is at the heart of this interrelation. Arthritis is an inflammatory condition which increases levels of free radicals. These toxic compounds can induce an oxidative state and affect multiple systems, including the cardiovascular system. Free radicals can damage the endothelium, leaving patients at a high risk for both hypertension and CVD. Therefore, arthritic pain can be simultaneously experienced with hypertension and other cardiovascular risks (Weber, 2009). High blood pressure can cause endothelial damage and decreased NO levels. Nitric oxide is a gaseous molecule that causes relaxation of the smooth muscle cells in the blood vessels and the GI tract. We suggest that treatments involving anti-inflammatory NO based drugs can thus be beneficial in alleviating pain and inflammation associated with conditions such as arthritis and cardiovascular risk factors. This is due to NO expanding the blood vessels (vasodilation) and reducing the pressure on the walls of the endothelium.

Another interesting association revealed in our study is the strong association between vitamin D supplementation and depression. These findings were also reported by Penckofer et al. (2010), who found that individuals with vitamin D deficiency are also at risk for depression. As mentioned previously, vitamin D regulates inflammatory responses, and inflammation increases risk of mental ailments. In addition, vitamin D through vitamin D receptors, regulates the functions of genes involved in brain neurotransmitters (Ardesia, 2015).

Our data also shows that those who have depression are more likely to have anxiety. In fact, about 50 percent of people being treated for either anxiety or depression actually suffer from



a secondary comorbid anxiety or depressive disorder (Hirschfeld, 2001). Additionally, patients who do not supplement with omega-3 are more likely to be depressed. Omega-3 has a greater effect on depression than vitamin D. Omega-3 has anti-inflammatory properties, and mental distress (anxiety and depression) has been linked to neural inflammation (Fuller-Thomson, 2006).

There are a few limitations to our study. Our database collected information on all types of arthritis and did not specify the type. Regardless, all arthritis is linked to inflammation, and IBD is an inflammatory disease as well. The goal of our observational study was to bring forward unestablished links between inflammatory conditions, nutritional supplements, and comorbidities. Also, the collected information in the database did not delineate between the different types of hypertension, whether it is primary or secondary hypertension, which is another limitation to the study. Finally, our database did not account for whether patients had anxiety before or after they were diagnosed with IBD or if any other factors contributed to their mental status; this is a confounding variable in our study.

## Conclusions

The data generated by the Auto-CM reports new associations between comorbidities and nutritional supplements in patients with IBD, all of which could be areas for future research. The relationships between folic acid, vitamin D, and omega-3 to inflammatory conditions of the GI tract are developing and are important factors to take into consideration in future studies. Our results suggest that folic acid and vitamin D supplementation may confer benefits in reducing inflammatory processes, while lack of omega-3 could be potentially disadvantageous. Our data also suggests a moderate association ( $LS = 0.68$ ) between arthritis, hypertension and CVD that could also be a new direction for research.

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