Micronutrients in IBD

Kaila Stephens
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

Abstract

Objective: To summarize rates of supplement adherence in youth with inflammatory bowel disease (IBD) and to identify predictors and outcomes of supplement adherence.
Methods: 49 adolescents (age 11-18) participated. Youth completed six monthly assessments of adherence and supplement knowledge. Youth and parents completed questionnaires. Medical record reviews provided medical and laboratory data.
Results: Mean supplement adherence rates ranged from 32% to 44%. Predictors of supplement adherence included higher knowledge (for multivitamin, iron, and calcium adherence) higher family involvement (for iron and calcium adherence), and greater inflammation (via a hematological index) for multivitamin adherence. Few relationships between supplement adherence and inflammation, growth, or nutritional outcomes were found.
Conclusion: Supplement adherence is problematic in pediatric IBD, and predictors of adherence were primarily psychosocial rather than biological variables. Future research should focus on larger sample sizes and assessments of supplement adherence that do not rely solely on patient self-report.

Introduction

Overview of IBD

Inflammatory bowel disease (IBD) is an idiopathic autoimmune disorder that causes chronic inflammation in one or more sections of the gastrointestinal tract (Gore, Balthazar, Ghahremani, & Miller, 1996; Hommel & Baldassano, 2010). The location of the inflammation, as well as the depth of inflammation in the intestinal tissue can indicate one of three types of IBD: Chron's disease (CD), ulcerative colitis (UC), or intermediate colitis (Eiden, 2003; Gore et al., 1996). In CD, inflammation may be present in any location from mouth to anus, yet in a majority of cases it is found in the terminal ileum. When diagnosing CD, the gastroenterologist will look for inflammation of the mucosa lining, epithelium invaded with neutrophils, and granuloma formation, which are indicative of CD (Eiden, 2003; Gore et al., 1996). This is unlike UC, in which patients experience inflammation localized mainly in the mucosa of the colon and rectum (Eiden, 2003; Gore et al., 1996). Indeterminate colitis is diagnosed when physicians cannot clearly distinguish between CD and UC. Guindi and Ridell (2004) found these patients are often later diagnosed with CD or UC.

Patients with IBD experience a number of primary symptoms caused by the disease and secondary symptoms caused by IBD medication. Primary symptoms include diarrhea, abdominal pain, fatigue, loss of appetite, weight loss, anemia, stunted growth, and delayed puberty. Secondary symptoms include: cushingoid appearance, weight gain, pancreatitis, and increased risk of cancer (Hommel, Denson, Crandall, & Mackner, 2008). Physicians apply a combination of symptoms, clinical examination, laboratory indices, radiology, endoscopy, and histology to make the diagnosis, to assess severity, and to predict the outcome of disease (Vermeire, Van Assche, & Rutgeerts, 2006). Unfortunately, there is not one nutritional formulation for disease management that works for all patients. Instead, physicians must closely observe changes in patients' weight, eating habits, and gastrointestinal (GI) symptoms (Eiden, 2003). The annual incidence of CD in children is 48 out of 100,000. The annual incidence of UC in children is 29 out of 100,000 (Kappelman, Moore, Allen, & Cook, 2012). The large number of individuals afflicted by IBD demonstrates a necessity to explore the many challenges faced by IBD patients.

Medication Adherence in IBD

Medication adherence is defined as the extent to which a patient follows the guidelines given by their physician or health care team regarding their medical regimen (Stockwell-Morris & Schulz, 1992). Across multiple pediatric conditions, nonadherence rates of approximately 50% are the norm and nonadherence is considered the greatest cause of treatment failure among those with chronic medical conditions (Quittner, Modi, Lemanek, Landis, & Rapoff, 2008). Treatment regimens of IBD patients are often complex, sometimes involving multiple medications with varying dosing schedules and pill quantities, nutritional supplements, dietary modifications, medications delivered via infusions, clinic visits, and surgery (Hommel et al., 2008). Regimen complexity and other psychological factors likely combine to make treatment adherence challenging. Several studies have explored behavioral and family functioning in pediatric IBD, but few studies have focused on treatment adherence in IBD (Hommel et al., 2008). Existing studies of treatment adherence in pediatric IBD have focused primarily on adherence to oral IBD maintenance medications (i.e., medications taken to sustain disease remission). As summarized by Hommel et al., (2008), the prevalence of nonadherence to oral medication in IBD ranges from 38% to 66% depending on the type of medication and method of adherence assessment used.

Little is known about adherence to dietary supplements among youth with chronic illnesses, particularly those with IBD. Potential differences in supplement adherence and medication adherence may be attributed to a number of barriers unique to supplements including: larger pill size compared to IBD medications, bad taste of pill, lack of knowledge about the purpose of the supplement, disease activity, experience of symptoms, and differences in child and parent involvement in supplementation versus primary IBD medications (Greenley, Stephens, Doughty, Raboin, & Kugathasan, 2010; Hommel & Baldassano, 2010; Ingerski et al., 2010). Factors that influence IBD medication adherence may also influence adherence to supplements.

Kitney et al. (2009) investigated rates of supplement (multivitamins, vitamin D, iron, calcium, fish oil, and other herbal supplements) adherence and reasons given by patients for nonadherence to supplements. Adherence to supplements ranged from approximately 11% to 58 %, with fish oil having the lowest adherence rate and vitamin D having the highest adherence rate (Kitney et al., 2009). Reasons participants gave for nonadherence to their supplements included being too busy, it involved taking too many pills, and their supplements made them feel sick (Kitney et al., 2009). Additional research is necessary to validate these findings and to understand other factors that can affect supplement adherence

Relevance of Supplement Adherence in Pediatric IBD

It is important to look at supplement adherence in adolescents because disease and medication side effects associated with IBD can cause nutritional deficiencies. Because adolescents are still developing, nutritional deficiencies may have implications for short and long-term health including lack of attainment of full height potential and development of bone disease (Moeeni & Day, 2011). Thus, oral micronutrient supplementation has been one medical treatment option to prevent or treat nutritional deficiencies.

Nutritional Deficiencies in IBD

Patients with IBD experience many specific nutritional deficiencies including iron and calcium deficiencies. Many IBD patients have one or more episodes of anemia, resulting from iron deficiency. Patients can also experience more subtle iron deficiencies that are below the threshold for a diagnosis of anemia (Bager al., 2011). Across multiple studies it has been found that the approximate prevalence of anemia in IBD (30%) is only slightly lower than the approximate prevalence of iron deficiency (45%) (Munoz, Gomez-Ramirez, & Garcia-Erce, 2009). A lack of iron effects multiple essential physiological functions including oxygen transport. Iron deficiency can be exacerbated by chronic disease symptoms. IBD associated anemia is most often caused by blood loss from the bowel or decreased iron absorption due to inflammation of the digestive tract (Bager et al., 2011; Eiden, 2003). Hematological evaluations for anemia consist of a complete blood count, which includes hemoglobin (HGB), hematocrit (HCT), and iron indices such as mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH) (Strople & Gold, 2008; Zemel, 2008). Physicians define anemia via low levels of hemoglobin or hematocrit (Strople & Gold, 2008).

Many physicians will delay iron therapy at the time of diagnosis because anemia can resolve concurrently with IBD symptoms (Gurram, Joeckel, & Stephens, 2012). However, it can be difficult to correct iron deficiency without iron supplementation or a high iron diet (Eiden, 2003). Due to the fact that iron deficiency and anemia can have a large impact on adolescent quality of life, motivation to adhere to supplements specific to this deficiency may be higher relative to youth with no symptoms (Rapoff, 2010). Additionally, adherence to iron supplements can result in a decrease in symptoms and fewer laboratory abnormalities (Eiden, 2003). Therefore, iron supplement adherence can have profound implications for improving quality of life. This is especially true for patients experiencing high disease activity.

Many patients with IBD also suffer from calcium deficiency. Inadequate intake and absorption of calcium is a mechanism by which skeletal disorders can develop. Skeletal disorders result from decreased bone density as well as chronic inflammatory and autoimmune diseases (Peterlik & Cross, 2005). Decreased bone mineral density results from multiple factors in patients with IBD. Medications such as corticosteroids, vitamin D and calcium deficiency, malabsorption, and inflammation are considered contributing factors to declining bone mass in IBD patients. (Eiden, 2003; Thayu, Semeao, & Leonard, 2008). Prednisone, a common drug for IBD patients, has been found to cause calcium loss because it leads to vitamin D resistance (Eiden, 2003). It is recommended that adolescents with IBD incorporate calcium and vitamin D supplementation as well as exercise into their regimens to prevent bone disorders (Thayu et al., 2008). Several studies have shown that calcium supplementation aids in child and adolescent bone formation (Thayu et al., 2008). In a small sample of patients diagnosed with multiple sclerosis, calcium, vitamin D, and magnesium supplementation decreased the relapse rate and had protective effects against colorectal cancer development (Peterlik & Cross, 2005). These results indicate adding calcium supplements into an IBD regimen is essential to overcoming the many barriers that patients face in calcium absorption in relation to bone health.

Disease Activity in IBD

Disease activity in the context of IBD is a multidimensional construct that can be assessed through serum biomarkers of inflammation, patient report, and physician evaluation. The presence of inflammation is one indicator of disease activity and is verified through serum biomarkers levels. Level of inflammation is used for diagnosis, determining disease activity, predicting relapse and assessing the effect of treatment (Lok et al., 2008). C-reactive protein (CRP) and erythrocytic sedimentary rate (ESR) elevate in the presence of inflammation, and are two commonly used measures (Rees & Gibson, 2011). CRP is the most commonly used biomarker for indication of acute and chronic inflammation (Rees & Gibson, 2011). CRP is an important protein produced by hepatocytes during an innate immune response, indicating inflammation or infection in various organs (Laihia, Koskinen, Waris, & Jansen, 2005; Vermeire et al., 2006). After detection of inflammation, hepatocytes are upregulated by three cytokines which increases the amount of CRP produced by the liver (Vermeire et al., 2006). Monitoring CRP levels is important for health providers to predict disease relapse. This can encourage physicians to stress to patients the importance of adherence to their medical regimens.

Another biomarker of inflammation is ESR. ESR is the rate at which erythrocytes migrate through the plasma (Vermeire et al., 2006). Normally, erythrocytes have a net negative charge and repel one another, which keeps the sedimentary rate high (Husain & Kim, 2002). Fibrinogen, a protein important for coagulation, forms bonds between platelets and becomes elevated during inflammation adding a positive charge to the serum (Husain & Kim, 2002). During times of inflammation, erythrocytes and fibrinogen attract one another and sedimentary rates decrease. An abnormal ESR can be indicative of non-specific inflammation (Vermeire et al., 2006). Unlike CRP, changes in ESR are prolonged rather than immediate (Vermeire et al., 2006). Because CRP levels can provide valuable information about current levels of inflammation and disease activity, and ESR levels provide information about chronic inflammation, both measures are important when assessing inflammation

Other methods of assessment of disease activity in the context of IBD are patient reports and physician report via physician global assessment (PGA). These assessments may affect adherence. Patients are accurate in identifying disease activity (Rapoff, 2010). Asthma and cystic fibrosis patients, who have more frequent and severe symptoms, and those with higher disease activity, are typically more willing to adhere to medication regimens than patients with fewer, less severe symptoms and lower disease activity (Rapoff, 2010). In addition, patient and parental perceptions of disease severity have proved to be more useful predictors of adherence than those of providers (Rapoff, 2010). Physician global assessment has been found to be very accurate in identifying levels of disease activity as indicated by high agreement between different physician raters (Hyams et al., 1991) PGAs have also been shown to have high agreement between physician ratings and other measures of disease activity that rely on laboratory values, medical exam results, and patient report. As found by Sewitch et al. (2003), disease activity predicts medication nonadherence in adult populations with IBD.

Nutritional & Growth Impairment in IBD

Growth impairment affects 15% to 40% of children with CD, while only 3% to 10% of adolescents with UC experience growth impairment (Gurram et al., 2012; Newby et

*This author wrote the paper as a part of a senior thesis under the direction of Dr. Greenley at the Rosalind Franklin University of Medicine and Science

al., 2008). Growth impairment at time of diagnosis or growth failure as an outcome of disease is more common in CD patients than in patients with UC (Moeeni & Day, 2011). This is mainly due to nutritional deprivation brought on by malabsorption and increased permeability of the ileum (Eiden, 2003; Moeeni & Day, 2011; Sturniolo, Di Leo, Ferronato, D'Odorico, & D'Inca, 2000; Vasseur et al., 2010). Paerregaard and Uldall-Urne (2005) found that the children with UC did not have any growth impairment when compared to controls. Additionally, they reported 50% of those with CD had a height below the 25th percentile for their age and sex. Growth impairment in IBD is often due to disease activity, including inflammation. In studies using mouse models, it was found that 40% of growth impairment resulted from gut-produced inflammatory protein molecules such as Interleukin-6 and tumor necrosis factor-alpha, both of which suppress levels of insulin-like growth factor (Moeeni & Day, 2011; Newby et al., 2008). Since IBD symptoms have severe implications regarding growth, it is vital to explore methods that can counteract growth impairment.

There are many causes of malnutrition and growth failure in pediatric IBD, including poor appetite, dietary restrictions, disease location, malabsorption, intestinal loss, drug-nutrient interaction, medication induced metabolic and hormonal change, and psychological disturbance (Eiden, 2003; Gurram et al., 2012). Nearly 90 percent of patients with CD experience malnutrition (Gurram et al., 2012). Poor nutrition and malabsorption can contribute to growth failure in IBD (Newby et al., 2008; Zemel, 2008). Growth status is an accurate indicator of well-being and nutritional status in adolescents (Zemel, 2008). Vasseur et al. (2010) investigated growth impairment and malnutrition in children with CD. They found that 9.5% of their sample experienced growth impairment and 32% experienced malnutrition. A follow up conducted six years after diagnosis found that 6.9% of the sample had growth impairment and 15% of the sample had malnutrition (Vasseur et al., 2010). Malnutrition and other morbidities provide reasoning for increased supplementation in adolescents with IBD

Predictors of Adherence

A number of studies have examined factors associated with higher adherence in IBD populations and among patients with other chronic medical conditions. Predictors can be grouped into two broad categories: biological or disease-related factors and psychosocial factors. With respect to biological factors, disease activity has been one factor that has been examined in relation to adherence. Stockwell-Morris and Schulz (1992) found that the presence of symptoms as reported by the patient predicted levels of nonadherence. Rapoff (2010) reviewed findings that indicated that higher disease activity was related to higher adherence among children with juvenile rheumatoid arthritis and asthma. Disease of longer duration also tended to be associated with lower adherence (Rapoff, 2010).

With respect to psychological factors, both knowledge and patterns of family involvement have been investigated as predictors of adherence. Alm-Roijer, Stagmo, Uden, and Erhardt (2004) found that patients diagnosed with coronary heart disease had better adherence to required lifestyle changes and treatment when they had a higher degree of knowledge regarding disease risk factors. Additionally, knowledge of one's disease and regimen was found to be important, but not sufficient for medication adherence (Hommel et al., 2013). Anderson, Auslander, Jung, Miller, and Santiago (1990) found higher nonadherence in adolescents with diabetes mellitus when there was a misunderstanding or disagreement in medical regimen responsibilities between parents and youth. Decreased supervision of adherence, with assumption of increased adolescent responsibility and involvement, was related to increased age. Similarly, when expectations for self-administration of asthma medication were developmentally inappropriate, poorer adherence was a result (Walders, Drotar, & Kercsmar, 2000). Therefore, there are many factors that must be considered when attempts are made to improve nonadherence in adolescents with IBD.

Gaps in Current Research

Although substantial research addresses nonadherence to oral medication in pediatric IBD, little research exists examining rates of nonadherence to supplements in the same population. This is noteworthy, given that medical professionals and researchers have regularly discussed the necessity for supplementation in medical regimens of IBD. Furthermore, little is known about predictors of higher levels of supplement adherence. No research currently exists investigating potential beneficial outcomes of higher levels of supplement adherence such as growth, nutrition, and disease status. Thus, the focus of this study was on analyzing both biological and psychosocial predictors of adherence as well as biological outcomes of adherence relevant to adolescents with IBD.

Whenever possible, multiple measures of these predictors and outcomes were used to acquire the most comprehensive picture of the construct. A limitation of many past IBD studies is the use of a wide age range of participants. To address this limitation, the current study focused on adolescents, a group that has an increased risk for nonadherence, and therefore potentially long-term deleterious health effects. In addition, most past studies that have examined adherence, including the Kitney study of supplement adherence, have collected data at just one time point (Kitney et al., 2009). In contrast, this study is strengthened by its longitudinal approach, as it examines adherence over a relatively long period of time (i.e., 6 months), giving a more stable and comprehensive estimate of adherence, rather than the cross sectional approach as used by Kitney et al. (2009). This research also examines adherence to three of the most commonly used supplements in pediatric IBD separately, rather than examining supplements as a single category.

Current Study Aims and Hypotheses

Aim 1

Aim 1 was to summarize rates of multivitamin, iron, and calcium adherence within the sample of youth with IBD. It was hypothesized that rates of adherence to supplements would be similar or slightly lower than previously documented medication adherence rates in this sample population (i.e., 90% or higher; Greenley et al., 2012).

Aim 2

Aim 2 was to examine the role of specific biological and psychological factors in predicting adherence to supplements in youth with IBD (both individually and combined). Specific predictor domains of interest include: a) youth knowledge of the need for supplementation; b) baseline disease activity indices based on physician report, patient report, and laboratory hematological markers of inflammation; c) specific laboratory-based indices of nutritional deficiencies based on hematological markers of iron deficiency and low total calcium at baseline, and d) high levels of both parent and child involvement in disease management at baseline. It was hypothesized that 1) higher

knowledge of reasons for taking the supplement would be associated with higher adherence during study participation; 2) higher levels of disease activity via PGA and patient report, and greater proportion of hematological lab abnormalities indicating inflammation at baseline would be associated with higher adherence during study participation; 3) a greater proportion of nutrient-specific hematological lab abnormalities in the year preceding study participation would be associated with higher adherence during study participation; and 4) high levels of both parent and child involvement in disease management at baseline would be associated with higher rates of supplement adherence during study participation.

Aim 3

Aim 3 was to examine relationships between supplement adherence during the study, disease, and linear growth outcomes during the 12 months following study participation. Specific outcomes of interest included: a) indices of disease activity based on patient report at 6 month follow up and laboratory hematological markers of inflammation in the 12 months after study participation; b) specific laboratory-based indices of nutritional deficiencies based on hematological markers of iron deficiency and low total calcium in the 12 months after study participation; and c) linear growth improvement in the 12 months following study participation. It was hypothesized that, 1) higher adherence during the study would be associated with lower levels of disease activity based on patient report of symptoms at the 6 month follow up, as well as a lower proportion of hematological lab abnormalities indicating inflammation in the 12 months following study participation; 2) higher adherence during the study would be associated with a lower proportion of hematological lab abnormalities in the year after study participation; and 3) higher adherence during the study would be associated with linear growth improvement in the 12 months after study participation.

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