4-16-2013

Micronutrient Supplementation in Pediatric Inflammatory Bowel Disease: Examining Predictors and Outcomes of Supplement Adherence

Kaila A. Stephens
Lake Forest College, stephka@lakeforest.edu

Micronutrient Supplementation in Pediatric Inflammatory Bowel Disease: Examining Predictors and Outcomes of Supplement Adherence

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 (ages 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 tended to be psychosocial rather than biological variables. Future research with larger sample sizes and assessments of supplement adherence that do not rely solely on patient self-report are important next steps.

Document Type
Thesis

Distinguished Thesis
yes

Degree Name
Bachelor of Arts (BA)

Department or Program
Biology

First Advisor
Lynn C. Westley

Second Advisor
Anne E. Houde

Third Advisor
Robert B. Glassman

LAKE FOREST COLLEGE

Senior Thesis

Micronutrient Supplementation in Pediatric Inflammatory Bowel Disease: Examining Predictors and Outcomes of Supplement Adherence

by

Kaila A. Stephens

April 16, 2013

The report of the investigation undertaken as a
Senior Thesis, to carry two courses of credit in
the Department of Biology

_____	_____
Michael T. Orr	Lynn C. Westley, Chairperson
Krebs Provost and Dean of the Faculty	
	_____
	Anne E. Houde
	_____
	Robert B. Glassman
	_____
	Rachel Neff Greenley

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 (ages 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 tended to be psychosocial rather than biological variables. Future research with larger sample sizes and assessments of supplement adherence that do not rely solely on patient self-report are important next steps.

Acknowledgments

I would like to express my very great appreciation to my thesis supervisor, Dr. Rachel Greenley, for her constant encouragement, intelligent guidance, and unwavering patience, during the planning and execution of this research work. Her willingness to give her time has been very much appreciated and will not be forgotten.

I would also like to acknowledge and thank my family, friends, and colleagues who have supported and encouraged me throughout my study.

In memory of Professor Robert B. Glassman.

Table of Contents

List of Abbreviations

CDC	Center for Disease Control and Prevention
CRP	C-reactive protein
CD	Crohn's disease
DEXA	Dual-energy X-ray absorptiometry
ESR	Erythrocytic sedimentary rate
GI	Gastrointestinal
HCT	Hematocrit
HGB	Hemoglobin
IBD	Inflammatory bowel disease
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MAM	Medication Adherence Measure
PCDAI	Pediatric Crohn's Disease Activity Index
PGA	Physician Global Assessment
RBC	Red blood cell
SPSS	Statistical Package for Social Sciences
UC	Ulcerative colitis

Introduction

Overview of IBD

Inflammatory bowel disease (IBD) is an idiopathic autoimmune disorder, which 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 (Eiden, 2003; Gore et al., 1996). In Crohn's disease (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 ulcerative colitis (UC), in which patients experience inflammation localized mainly in the mucosa of the colon and rectum (Eiden, 2003; Gore et al., 1996). Finally, indeterminate colitis is diagnosed when physicians cannot clearly distinguish between CD and UC. As summarized by Guindi and Ridell (2004), these patients often are diagnosed later with CD or UC.

Patients with IBD experience a number of primary symptoms caused by the disease and may also experience secondary symptoms caused by IBD medication. Symptoms patients can experience solely from disease include diarrhea, abdominal pain, fatigue, loss of appetite, weight loss, anemia, stunted growth, and delayed puberty. Symptoms caused by maintenance medications may 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, and endoscopy with 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 the 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, involving multiple medications with varying dosing schedules and pill quantities, nutritional supplements, dietary modifications, medications delivered via infusions, clinic visits, and sometimes 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, in general, or those with IBD, in particular. Potential differences in supplement adherence and medication adherence may be attributed to a number of barriers unique to supplements (compared to IBD medications) including: larger pill size or bad taste of pill, knowledge of why or for what purpose they are taking 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.

One previous study has examined supplement adherence. 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 that taking 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 in this population.

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. Since adolescents are still developing, nutritional deficiencies may have implications for short and long-term health including lack of attainment of full height potential and later development of bone disease (Moeeni & Day, 2011). Thus, oral micronutrient supplementation is one medical treatment option to prevent or treat nutritional deficiencies.

Nutritional Deficiencies in IBD

Patients with IBD experience many nutritional deficiencies in specific areas, including iron and calcium deficiencies. Many IBD patients have one or more episodes of anemia, which can be a result of 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 affects multiple essential physiological functions, the most common being oxygen transport. Iron deficiency can be exacerbated by chronic disease symptoms. Anemia in IBD 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) and hematocrit (HCT), and iron indices such as mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH) (Strople & Gold, 2008; Zemel, 2008).

Physicians define anemia by low levels of hemoglobin or hematocrit (Strople & Gold, 2008).

Many physicians will delay iron therapy at time of diagnosis because anemia can resolve on its own when IBD symptoms are resolved (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 negative symptoms and fewer laboratory abnormalities (Eiden, 2003). Therefore, iron supplement adherence can have profound implications for improving quality of life, especially if 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 may 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. Factors that contribute to declining bone mass include medications such as corticosteroids, vitamin D and calcium deficiency, malabsorption, and inflammation (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). Calcium, vitamin D, and magnesium supplementation decreased the relapse of a small sample of patients diagnosed with multiple sclerosis, and had protective effects against the development of colorectal cancer (Peterlik & Cross, 2005). Therefore, adding calcium supplementation into an IBD regimen is essential to overcome the many barriers that patients face in absorbing the correct amounts of calcium for bone health.

Disease Activity in IBD

Disease activity in the context of IBD is a multidimensional construct that can be assessed based on 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) are two commonly used measures that become elevated in the presence of inflammation (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 up regulated by three cytokines, increasing the amount of CRP produced by the liver (Vermeire et al., 2006). Monitoring CRP levels is important for health providers to predict disease relapse, and therefore may encourage them to stress to patients the importance of adherence to their medical regimens.

Another biomarker of inflammation, which can be utilized in determining disease activity, 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 therefore repel one another, keeping the sedimentary rate high (Husain & Kim, 2002). Fibrinogen, a protein important for coagulation, forms bonds between platelets and becomes elevated during inflammation, which adds a positive charge to the serum (Husain & Kim, 2002). Therefore, 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). Thus, when assessing inflammation, attention to both CRP and ESR levels is important because CRP levels can provide valuable information about patient's current level of inflammation/disease activity; whereas ESR levels provide information about chronic inflammation over an extended period of time.

Other methods of assessment of disease activity in the context of IBD are patient report or physician report via physician global assessment (PGA), and such assessment 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 adherent to their medication regimens than patients with fewer, less severe symptoms and lower disease activity, possibly in effort to improve their predicament (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 is also very accurate in identifying levels of disease activity as indicated by

high agreement between different physician raters (Hyams et al., 1991) and 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 has been found to predict 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 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) examined the effect IBD had upon growth in 99 Danish children diagnosed with either CD or UC. They discovered that the children with UC did not have any growth impairment when compared to standards. However, 50% of those with CD had a height below the 25th percentile for their age and sex (Paerregaard & Uldall-Urne, 2005). Growth impairment in IBD is often due to disease activity, including inflammation. In studies using mice models, it was found that 40% of growth impairment is the result of gut-produced inflammatory protein molecules such as Interleukin-6 and tumor necrosis factor-alpha, both of which can suppress levels of insulin-like growth factor (Moeeni & Day, 2011; Newby et al., 2008). Since IBD symptoms such as inflammation have severe

implications regarding growth, it is vital to explore methods such as nutritional supplementation that can counteract growth impairment.

Poor nutrition and malabsorption of nutrients are other manifestations of disease activity. 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 was conducted six years after diagnosis and it was found that 6.9% of the sample had growth impairment and 15% of the sample had malnutrition (Vasseur et al., 2010). Malnutrition alone is an adequate reasoning for supplementation in adolescents with IBD. Therefore adherence to supplementation is important to prevent onset of malnutrition and other morbidities.

Predictors of Adherence

A number of studies have examined factors associated with better 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 versus psychosocial factors. With respect to biological factors, disease activity has been one factor that has been examined in relation to adherence. For example, Stockwell-Morris

and Schulz (1992) found that the presence of symptoms as reported by the patient was a predictor 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 the risk factors for their disease. 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 current research examines 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. Similarly, no one has investigated potential beneficial outcomes of higher levels of supplement adherence such as growth, nutrition, and disease status. Thus, the focus of this study was on 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 a 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 to or slightly lower than previously documented medication adherence rates in this sample (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 of disease activity, 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 and 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.

Methods

Procedure

All participants were part of a larger longitudinal study that examined adherence to thiopurine, an oral IBD maintenance medication, in English-speaking IBD patients

between the ages of 11 and 18 years who had no other chronic medical condition for which they needed to take daily medication. All participants included in the current analyses were also taking one or more supplements (i.e., multivitamin, iron, or calcium) daily. These three supplements were examined specifically because they are among the supplements that are most commonly utilized by patients with IBD, and because they were the supplements most readily utilized by our sample. Patients, who fit the above inclusion criteria, were approached at the Children's Hospital of Wisconsin Gastroenterology Clinic. When they agreed to participate, children and parents provided consent or assent and completed the baseline questionnaires evaluating demographic information, disease symptoms, barriers to adherence, and youth and family functioning. At this time, youth also completed a validated semi-structured interview to assess their knowledge of and adherence to their medications and supplements, the Medication Adherence Measure (MAM) (Zelikovsky & Schast, 2008). This measure was also completed every month by participants via phone during the 6 months of study participation. Finally, patients were asked to complete questionnaires (similar to those completed at baseline) once more at the end of the 6 months of study participation.

For the current analyses, medical records were also reviewed to obtain information about patient disease activity, linear growth, nutrition and laboratory values for three time periods: one year prior to the larger longitudinal study, the 6 months during which time participants were enrolled in the study, and one year after the study.

Participants

Forty-nine of the 68 participants enrolled in the larger longitudinal study were included in this analytic sample. Those that were not included either withdrew from the

study prior to completing the 6 months of data collection, or they were not taking one of the three supplements of interest. Participants did not significantly differ from nonparticipants in age [t (66) = 0.50, p >. 05] or sex (Φ =0.09, p > .05).

Of the 49 participants, 29 were male (59%), 45 were Caucasian (92%), and 42 were diagnosed with Crohn's disease (86%). Participants ranged from 11-18 years old [*M (SD)* = 14.63 years (2.03 years)]. Thirty seven (76%) patients in our sample had no disease activity at baseline based on PGA rating, while nine (18%) had mild disease activity, and three (6%) had moderate disease activity.

The majority of participants (92%; n = 45) were taking a multivitamin, while fewer were taking calcium (49%; n = 24) or iron (35% n = 17) supplements. Most subjects were prescribed two supplements (59%; n = 29); fewer were taking only one supplement (33%; n = 16). Only 8% of the sample (n = 4) was on three supplements. Among the 16 youth taking one supplement, the majority (n = 13; 81%) was prescribed a multivitamin, with fewer prescribed iron (n = 2; 13%) or calcium (n = 2; 13%). The majority of the 29 youth prescribed two supplements were taking a multivitamin and calcium (n = 18; 62%), while the remainder was prescribed either a multivitamin and iron (n = 10; 35%) or calcium and iron (n = 1; 3%).

Measures

Demographics

Parents provided all demographic information at time of baseline assessment by completing a questionnaire. Information provided included adolescent age, gender, race/ethnicity, socioeconomic status, and age.

Adherence

Adherence was assessed based on patient self-report on the MAM (Zelikovsky & Schast, 2008), a semi-structured adherence interview. Patients were asked to report all supplements they were prescribed, as well as how many days in the past week they had missed a dose of each supplement. This information was retrieved at baseline, as well as at each of the monthly follow-ups. Adherence to each supplement was calculated as such: [(number of doses prescribed in a given week – number of doses reported missed in a given week) / number of doses prescribed in a given week] * 100. Each participant was given a total adherence score by averaging each monthly adherence score, for each supplement individually. For example, if a patient were prescribed a multivitamin and calcium, that patient would have two adherence scores calculated: 1) 6-month multivitamin adherence percent; and 2) 6-month calcium adherence percent.

Disease Activity

Self report of symptoms. Self-reported symptoms were obtained from each of the participants through baseline and 6 month follow up questionnaires. The IBD Symptoms Checklist was created for the larger longitudinal study based on the most common symptoms and medication side effects seen in IBD as reported by the Crohn's and Colitis Foundation of America (2013). A subset of symptoms was chosen as an index of disease activity in the present investigation based on those symptoms used in other measures of disease activity. The specific symptoms included in the patient-report of disease activity in the present study were abdominal pain, nausea, vomiting, sleepiness, dizziness, diarrhea, loss of appetite, and fever. Patients reported if they had experienced any of the symptoms in the past four weeks, in a yes or no response. Yes responses were coded as 1,

while no responses were coded as 0. The total number of symptoms endorsed was summed to create a total disease activity score for each participant. Higher disease activity scores reflected an increased number of symptoms.

Physician global assessment of disease activity. At enrollment, a PGA rating of disease activity was acquired for each patient to determine disease activity. PGA ratings give an indication of disease activity based on a four-point rating scale where 0 is no symptoms, 1 is mild, 2 is moderate, and 3 is severe disease activity. PGA ratings have been shown to be consistent with the Pediatric Crohn's Disease Activity Index (PCDAI) and other more complex measures of disease activity (Hyams et al., 1991).

Hematological biomarkers of inflammation. All hematological values were retrieved from laboratory blood draws throughout the 12 months prior to the study (pre study) and during the 12 months after participants had completed the study (post study). Each biomarker was abstracted from the patient's medical record and analyzed separately for each participant. Hematological biomarkers of inflammation included CRP and ESR. Since participants may have had more than one lab draw during the pre study or post study periods, the proportions of abnormal CRP and ESR values were computed for the pre study and post study periods. Proportions of abnormal CRP and ESR were calculated identically, but separately. First, the total number of abnormal CRP or ESR lab values was summed for each participant, for each biomarker, during each time interval (pre study or post study). Second, the total number of CRP or ESR lab values available was summed for each participant, for each biomarker, during each time interval (pre study or post study). The proportion reflected the number of abnormal lab values divided by the total number of lab values available during the given time interval. Thus, each

participant was given an abnormal lab proportion for each biomarker in each time interval that was used for analyses, resulting in 4 proportions for each participant—Proportion of abnormal CRP values pre study, proportion of abnormal ESR values pre study, proportion of abnormal CRP values post study, and proportion of abnormal ESR values post study.

Hematological Indices of Nutritional Status

All nutritional outcomes were assessed via hematological lab values available in participant medical records. Lab values were retrieved from blood draws performed throughout the 12 months prior to the study (pre study) and during the 12 months after participants had completed the study (post study). Hematological indices included nutritional labs specific to calcium and iron supplementation, and biomarkers indicative of inflammation. The lab value that was specific to calcium supplementation was baseline total calcium. Several baseline hematological indices were used for predicting iron deficiency including: red blood cell count (RBC), HGB, HCT, MCV, and MCH levels. A single iron deficiency score was calculated for each participant.

For both calcium and iron nutritional deficiencies, a proportion was calculated to reflect the number of abnormal lab values compared to the total number of lab values available during the period (either pre study or post study). First, the total number of abnormal calcium or iron-related lab values was summed for each participant during each time interval (pre study or post study). Second, the number of total calcium or iron-related lab values was summed for each participant during each time interval (pre study or post study). The proportion reflected the number of abnormal lab values divided by the total number of lab values available during the given time interval. Thus, each

participant was given an abnormal lab proportion for calcium and iron in each time interval that was used for analyses, resulting in 4 proportions for each participant—Proportion of abnormal iron-related values pre study, proportion of abnormal calcium values pre study, proportion of abnormal iron-related values post study, and proportion of abnormal calcium values post study.

Knowledge

Supplement knowledge was assessed using the MAM at baseline and at each monthly follow up (Zelikovsky & Schast, 2008). Participants were asked the following question: "What kind of medicine is this?" for each of the supplements that they were prescribed. Patients' responses were recorded verbatim and later placed into one of three knowledge categories, which were developed by this student and her thesis mentor. Categorization was completed for each supplement separately. Categories were developed based on degree of knowledge of their supplements, with Category 1 being the least sophisticated response and Category 3 reflecting the most sophisticated response. Children whose responses fell into Category 1 indicated that they did not know what the supplement was for (i.e. "I don't know"). Children whose responses fell into Category 2 listed the name of supplement or described a nonspecific way the supplement was helpful to them (i.e. "Calcium" or "It makes me healthy"). Responses that fell into Category 3 reported a specific way that the supplement helped their health, body, or IBD symptoms (i.e. "Helps my inflammation"). Two raters coded all responses and inter-rater agreement for response categorization was 98%. Any discrepancies were resolved by discussion. For the purposes of the analyses, we used the most sophisticated response given by a given participant over the full study interval as their measure of knowledge in the analyses.

Parent and Child Involvement in Supplement Taking

Parent and child involvement was measured with the Inflammatory Bowel Disease Family Responsibility Questionnaire at time of enrollment (Greenley et al., 2010). Youth answered item 24 of the questionnaire: "How involved is each family member in making sure you are getting a daily multivitamin or nutritional supplement". Children rated their own involvement as well as their perception of their mother's involvement on a 0 to 3 scale. Families were placed into either high or low involvement groups. High involvement was defined as a score of 2 or 3 for both mother and child (2 is defined as "somewhat involved"; 3 is defined as "involved almost all the time"). If either individual had a low involvement rating (0 or 1), the family would be included in the low involvement group.

Growth Improvement

Growth improvement of each participant during the 12 months following study participation was calculated via a standard means of computing growth velocity. To calculate growth velocity, each patient's height (in centimeters) was recorded at the 6-month follow up and again at 12 months after study completion. Next, average height for each participant's age and sex was abstracted from Center for Disease Control and Prevention (CDC) growth tables (CDC, 2009). Two z-scores were then computed: a) z_1 = (Height at 6 month follow up) – (Average height for age and sex) / (Standard deviation of height from CDC); and b) z_2 = (Height 12 months after completion of study) – (Average height for age and sex) / (Standard deviation of height from CDC). In accord with standard definitions used in other pediatric IBD research (Walters & Griffiths, 2008), if

the difference between z_1 and z_2 scores was ≥ 0.5 standard deviation units, that participant was considered to have growth improvement.

Analytic Plan

All analyses were performed using IBM's Statistical Package for Social Sciences (SPSS), version 17.0.

Aim 1 Analyses

To summarize rates of supplement adherence within the sample of youth with IBD, mean levels of supplement adherence, standard deviations, and ranges of adherence scores were computed for each supplement.

Aim 2 Analyses

Aim two sought to examine the role of biological and psychological factors in predicting adherence to supplements in youth with IBD (both individually and combined). Specific predictors of interest included: a) knowledge of the need for supplementation; b) general disease activity indices; c) specific laboratory-based indices of nutritional deficiencies and d) family involvement.

To examine knowledge as a possible predictor of adherence, mean differences in levels of adherence across the three different knowledge categories were measured using an ANOVA. Effect size analyses were conducted to determine the magnitude of differences in adherence between the three knowledge categories because of the small sample size. To compute effect sizes, we calculated Cohen's d. This statistic looks at the differences between two means divided by the standard deviation. A d value of .20 = a small effect size, a d value of .50 = a medium effect size, and a d value of .80 = a large effect size. In psychological research, most researchers agree that a medium effect size is

one that suggests a meaningful real-world difference between groups. We conducted effect size analyses because of our small sample size, which made obtaining p values < .05 difficult.

To examine disease activity as a possible predictor of adherence, the following analyses were conducted: a) correlations between patient report of symptoms at baseline and adherence; b) correlations between physician report of disease activity at baseline and adherence; c) correlations between proportion of hematologic markers of inflammation (CRP and ESR) in the year prior to study participation and adherence during the study for each supplement separately.

To examine the possible association between proportion of nutrition related laboratory abnormalities in the year before study participation and adherence, correlations were run to test for a significant relationship. Specific nutritional lab abnormalities investigated were: total calcium, HGB levels, RBC count, HCT levels, MCV, and MCH levels.

Finally, correlations were run to examine the possible relationship between family involvement and supplement adherence during study participation, for each supplement separately. Participants were grouped into one of two categories based on family involvement (high involvement of both mother and child or lack of high involvement of both mother and child).

To examine the combined influence of multiple biological and psychological factors on supplement adherence, regression analyses were conducted. Regression models containing multiple independent variables were examined as predictors of supplement adherence. Predictor variables were included in these regression models if

they were correlated at r = .30 or higher with adherence (the equivalent of a medium effect size). Separate regression analyses were conducted for each of the three supplements.

Aim 3 Analyses

The goal of Aim 3 was to examine relationships between supplement adherence during the study and disease and growth outcomes during the 12 months following study participation. Specific outcomes of interest were: a) indices of disease activity; b); presence of hematologic lab abnormalities associated with specific nutrient deficiencies; and c) growth improvement.

To examine the possible relationship between adherence during the study with disease activity after study participation, correlations were run between adherence during the study and youth reported symptoms at 6 month follow up. Correlations were also run between adherence during the study and proportion of hematologic markers of inflammation (CRP and ESR) in the year following study participation.

To study possible associations between adherence during study participation and proportion of nutritional lab abnormalities in the 12 months following study participation, two correlations were run. The first correlation examined associations between the proportion of calcium specific lab abnormalities and adherence rates. The second correlation examined associations between the proportion of iron specific lab abnormalities and adherence rates. Specific nutritional lab abnormalities investigated were: total calcium, HGB levels, RBC count, HCT levels, MCV, and MCH levels.

Finally, correlations were run between adherence during study participation and growth improvement in the 12 months following study participation to test for possible

significant relationships. For these analyses, participants were coded as showing growth improvement versus no evidence of growth improvement.

For all analyses related to Aims 2 and 3, each supplement was examined separately. In addition, because of the small sample size, we did not rely solely on p values to determine significance of findings (since with a small sample size, we were at an increased risk of making a Type I Error). Rather, any findings meeting criteria for a medium effect size (e.g., bivariate or semi-partial correlations of .30 or higher) were considered to be meaningful findings.

Results

Aim 1 Results

Aim 1 summarized rates of adherence to multivitamin, iron, and calcium supplements (Table 1). Mean adherence to multivitamin, iron, and calcium regimens ranged from 32% to 44%. Mean multivitamin adherence was 36.47% $\pm$ 30.77 SD, mean iron adherence was 44.19% $\pm$ 34.86 SD, and mean calcium adherence was 31.67% $\pm$ 27.85 SD in the sample. Supplement adherence was well below average adherence of 93-98% to prescribed oral medication in a similar population (Greenley et al., 2012). Thus, our finding of mean supplement adherence rates of 32% to 44% was not consistent with the hypothesis that supplement adherence rates would be similar to or slightly lower than published oral medication adherence rates. Instead, they were much lower than oral medication rates.

Table 1.

Mean, Standard Deviation, and Range Statistics for Rates of Adherence to Supplements

Supplement	X	*SD*	Range	*N*
Multivitamin	36.47	30.77	0-93.88	45
Iron	44.19	34.86	0-100	17
Calcium	31.67	27.85	0-91.84	24

Aim 2 Results

Aim 2 examined the role of specific biological and psychological factors in predicting adherence to supplements in youth with IBD. We examined relationships between predictors and adherence both individually and combined. Specific predictors examined included: 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 at baseline, and d) level of parent and child involvement in disease management at baseline (coded as high or low involvement). Because of the small sample size, we did not rely solely on p values to determine significance of findings (since with a small sample size, we were at an increased risk of making a Type I Error). Rather, any findings meeting criteria for a medium effect size (e.g., correlations of .30 or higher) were considered to be meaningful findings.

Knowledge and Adherence

One-way ANOVAS were conducted to examine the relationship between knowledge (categorized into low, moderate, and high groups) and adherence to multivitamin, iron, and calcium supplements (Figure 1). Knowledge had a significant main effect on adherence for all three supplements. First, knowledge had a main effect on multivitamin adherence [F (2, 42) = 21.29, $p < .01$]. Follow up analysis results showed that those with low knowledge had lower multivitamin adherence (M = 7.00% SD = 14.95), than those with moderate (M = 44.71% SD = 26.38; d = 1.64), or those with high knowledge (M = 70.91% SD = 14.79; d = 4.29). Additionally, those with moderate knowledge had significantly lower adherence than those with high knowledge (d = 1.06). All effect sizes that examined differences in adherence between the three knowledge groups were large in magnitude. These findings were consistent with the hypothesis that higher knowledge of multivitamin supplement would be related to better adherence to a multivitamin supplement.

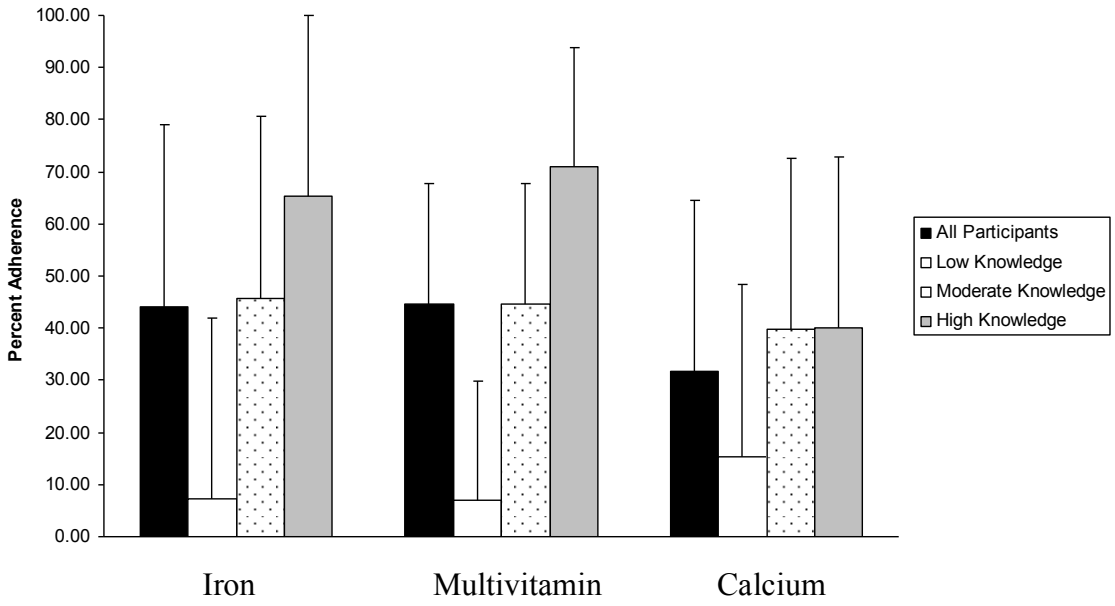

Figure 1. Mean rates of adherence to vitamin and mineral supplements for the total sample and by subgroups of participants based on supplement knowledge category. Standard deviations are represented in the figure by the error bars attached to each column.

Knowledge also had a main effect on adherence to iron supplements [F (2,14) = 5.48, $p < .05$] Results indicated that those with low knowledge had lower adherence (M = 15.36% SD = 22.93), than those with moderate (M = 45.71% SD = 32.95; d = 1.16), or those with high knowledge (M = 65.24% SD = 29.53; d = 1.85; Figure 1). The moderate knowledge group also had significantly lower adherence compared to the high knowledge group (d = 0.64). Effect sizes were found to be medium and large. These results support the hypothesis that higher knowledge of iron supplementation would be related to higher adherence to an iron supplement.

Finally, knowledge had a main effect on calcium supplement adherence [F (2,21) $p < .05$]. Analyses indicated that those with low knowledge had lower adherence (M = 7.14% SD = 17.50), than those with moderate (M = 39.68% SD = 30.00; d = 1.26), or those with high knowledge (M = 40.02% SD = 23.16; d = 1.55; Figure 1). Effect sizes

were large in magnitude, and therefore support the hypothesis stating higher calcium supplement knowledge is related to higher calcium supplement adherence. However, only a small effect size was found for the difference between the moderate and high knowledge group (d = 0.01) and therefore this comparison did not support the hypothesis.

Disease Activity and Adherence

With respect to disease activity as a predictor of adherence during the study, we used three different measures of disease activity: 1) baseline self-report of disease-related symptoms; 2) baseline physician's global assessment of disease activity; and 3) baseline laboratory hematological indicators of inflammation. Only one meaningful correlation between disease activity and adherence was found. Specifically, a meaningful correlation was found between abnormal CRP levels and multivitamin adherence ($r = .43$, $p > .05$), such that higher inflammation prior to the study predicted better multivitamin adherence during the study.

Correlations between self-reported symptoms and multivitamin adherence were not significant ($r = -.17$, $p > .05$). Correlations between self-reported symptoms and iron adherence were not significant ($r = .28$, $p > .05$). Correlations between self-reported symptoms and calcium adherence were not significant ($r = .24$, $p > .05$). Correlations across all three supplements were small in magnitude. Thus, the lack of significant findings was not due to the small sample size. The hypothesis that a higher number of self-reported symptoms of disease activity will predict higher adherence was not supported.

Additionally, no significant correlations were found between baseline physician's global assessment of disease activity and supplement adherence for all three supplements

(multivitamin adherence $r = -.09$, $p > .05$; iron adherence $r = -.02$, $p > .05$; and calcium adherence $r = .24$, $p > .05$). All three of these correlations failed to meet the cut off for a designation of a small effect size and thus were found to be or less than small in magnitude. Therefore, the hypothesis that physician's assessment of disease activity was associated with supplement adherence was not supported.

Regarding inflammation as a predictor of adherence to multivitamin, calcium, and iron adherence, two different baseline hematological indices of inflammation were used: CRP and ESR. No significant correlations were found between abnormal CRP levels and iron adherence ($r = .24$, $p > .05$), or between abnormal CRP levels and calcium adherence ($r = .01$, $p > .05$). Correlations between abnormal CRP levels and iron adherence, and abnormal CRP levels and calcium adherence were small effect sizes. No significant correlations were found between abnormal ESR and iron adherence ($r = .24$, $p > .05$), multivitamin adherence ($r = .02$ $p > .05$) or calcium adherence ($r = -.04$, $p > .05$). These correlations were small or less than small in effect size. Taken together, results examining CRP and ESR as measures of inflammation offered little support for the hypothesis that with an increased proportion of abnormal inflammatory markers present at baseline, there would be increased adherence to the three supplement categories throughout the study. Specifically, in only one of six analyses this hypothesis was supported.

Laboratory-Based Nutritional Abnormalities and Adherence

The presence of nutritional abnormalities the year prior to study participation was used to predict adherence to iron and calcium supplements during study participation. Nutritional abnormalities included factors indicative of iron deficiency (which were

correlated with iron adherence only) and total calcium (which were correlated with calcium adherence only). Regarding factors indicative of possible iron deficiency, the following hematological indices were used: HGB, RBC, HCT, MCV, and MCH. Correlations were run using the proportion of abnormal laboratory indices in the year prior to enrollment as the predictor. No significant correlation was found between presence of abnormal iron labs and iron adherence (r = -.12, p > .05). These findings did not support the hypothesis that those with a greater proportion of abnormal iron labs would have better adherence to iron supplements during the study.

Finally, patients' proportion of abnormal calcium lab values during the one-year before enrollment was examined as a possible predictor of calcium adherence. It was found that those with low total calcium one year prior to the study were not more likely to have higher adherence to a calcium supplement during the study (r = .27, p > .05). This finding did not support the hypothesis that those with a greater proportion of abnormal calcium labs present in the year prior to the study would have better adherence to their calcium supplement during the study.

Family Involvement and Adherence

Correlations were examined between youth and mother involvement at baseline and adherence to multivitamin, iron, and calcium supplements, respectively. Meaningful correlations were found between involvement and both iron adherence (r = .59, p < .05) and calcium adherence (r = .33, p > .05), while no meaningful correlation was found between multivitamin adherence and involvement (r = .29, p > .05); although the latter nearly reached criteria for a medium effect size and for statistical significance. The correlation between iron and involvement was medium in magnitude, and the correlation

between calcium adherence and involvement was small in magnitude. This supported the hypothesis that the group of families with high youth and mother involvement in administration of supplements would have higher adherence to those supplements compared to families in which one or both family members had low levels of involvement.

Regression Analyses

Linear multiple regression analyses were run in order to examine the combined impact of several of the above independent variables on supplement adherence. Analyses were run with all independent variables entered using simultaneous entry. Only independent variables with correlations of .30 or larger (the equivalent of medium effect sizes) with the dependent variable were chosen for inclusion in the regression analyses. Three regressions were run in total, one for each supplement dependent variable (i.e., multivitamin, iron, and calcium).

Results of a regression analysis in which multivitamin adherence was the dependent variable showed that multivitamin knowledge and proportion of abnormal CRP levels combined contributed 48.4% of the variance to the predication of multivitamin adherence, a statistically significant finding (Multiple $R = .70$; $F\ (12, 11) = 5.16$, $p < .05$; Table 2). After controlling for the impact of knowledge, proportion of abnormal CRP levels were not a statistically significant predictor of multivitamin adherence (β involvement = .35; $t = 1.59$, $p > .05$). However, when controlling for the effect of CRP abnormality, knowledge was a statistically significant predictor of multivitamin adherence (β involvement = .55; $t = 2.52$, $p < .05$). Examination of effect sizes by looking at the squared semi-partial correlations showed a medium effect size for

multivitamin knowledge (sr^2 = .30) and a small effect size for abnormal CRP (sr^2 = .12). These results support the hypothesis that combining independent variables would account for even more variance in multivitamin adherence than each of the independent variables alone (Table 2).

Table 2.

Predictors of Multivitamin Adherence

Independent Variable	B	β	t	sr^2
Multivitamin Knowledge	28.37	.55	2.52	.30
Abnormal CRP Lab Value	32.09	.35	1.59	.12
				R = .70
				R^2 = .48
				F = 5.16*

*p<.05; **p<.01; ***p<.001

For the regression analysis in which iron adherence was the dependent variable, iron knowledge and family involvement variables combined contributed 50.3% variance to the prediction of iron adherence, a statistically significant result (Multiple R = .71; F (2, 13) = 6.59, p < .05; Table 3). After partialling out the impact of family involvement, knowledge was not a statistically significant predictor of iron adherence (β knowledge =

.48; $t = 2.02$, $p > .05$). After partialling out the impact of knowledge, family involvement was not a statistically significant predictor of iron adherence (β involvement = .32; $t = 1.34$, $p > .05$). Examination of effect sizes by looking at the squared semi-partial correlations showed a small effect size for knowledge ($sr^2 = .16$) and a less than small effect size for involvement ($sr^2 = .07$). These results support the hypothesis that combining independent variables would account for even more variance in the prediction of iron adherence than each of the independent variables alone.

Table 3.

Predictors of Iron Adherence

Independent Variable	B	β	t	sr^2
Iron Knowledge	18.49	.48	2.02	.16
Mother and Child Involvement	28.24	.32	1.34	.07
				R = .71
				$R^2 = .50$
				F = 6.59*

*p<.05; **p<.01; ***p<.001

In a regression analysis in which calcium adherence was the dependent variable, calcium knowledge and family involvement variables combined accounted for 18.9% of the variance in the predication of calcium adherence. This finding was statistically

significant (Multiple $R = 0.55$; $F\ (2, 21) = 4.61$, $p < .05$; Table 4). After controlling for the effect of knowledge, family involvement was not a statistically significant predictor of calcium adherence (β involvement = .34; $t = 1.87$, $p > .05$). However, after controlling for family involvement, knowledge was a statistically significant predictor of calcium adherence (β involvement = .44; $t = 2.42$, $p < .05$). Effect sizes, determined by examining squared semi-partial correlations, were small for both calcium knowledge ($sr^2 = .19$) and family involvement ($sr^2 = .11$). These results support the hypothesis that combining independent variables would account for even more variance in calcium adherence than the each of the independent variables alone.

Table 4.
Predictors of Calcium Adherence

Independent Variable	B	β	t	sr^2
Calcium Knowledge	15.37	.44	2.42	.19
Mother and Child Involvement	20.41	.34	1.87	.11
				R = .55
				$R^2 = .31$
				F = 4.61*

*p<.05; **p<.01; ***p<.001

Aim 3 Results

Aim 3 examined relationships between supplement adherence during the study and disease and growth outcomes during the 12 months following study participation. Specific outcomes of interest included: a) indices of disease activity; and b) presence of hematologic lab abnormalities associated with specific nutrient deficiencies. Because of the small sample size, we did not rely solely on p values to determine significance of findings (since with a small sample size, we were at an increased risk of making a Type I Error). Rather, any findings meeting criteria for a medium effect size (e.g., correlations of .30 or higher) were considered to be meaningful findings.

Disease Activity and Adherence

When examining the relationship between supplement adherence during the study and disease activity outcomes, we used two different measures of disease activity: 1) presence of self-reported disease-related symptoms at the six month follow up; and 2) the proportion of abnormal hematological indicators of inflammation collected during the 12 months following study participation. No significant correlations were found between supplement adherence and self-reported disease symptoms for any of the three supplements (multivitamin adherence $r = -.09$, $p > .05$; iron adherence $r = -.01$, $p > .05$; and calcium adherence $r = .16$, $p > .05$). Correlations between multivitamin adherence and iron adherence with self-reported disease activity did not meet the cut off for a small effect size. The correlation between calcium adherence and self-report of disease activity was small in magnitude. These findings did not support the hypothesis that higher adherence would be related to the outcome of fewer self-reports of disease-related symptoms at the six-month follow up.

Correlations were also run to examine the relationship between supplement adherence during the study and indicators of disease inflammation as outcomes. The proportions of two different hematological indices of inflammation, CRP and ESR, collected during the year following study participation were used in analyses. A meaningful correlation was found between calcium adherence and proportion of abnormal CRP levels ($r = .35$, $p > .05$), yet no significant correlations were found between multivitamin adherence and proportion of abnormal CRP levels ($r = -.03$, $p > .05$), or between iron adherence and proportion of abnormal CRP levels ($r = -.07$, $p > .05$). The correlation between calcium adherence and proportion of abnormal CRP levels was found to be medium in magnitude. Correlations between multivitamin adherence and proportion of abnormal CRP levels, and iron adherence and proportion of abnormal CRP levels did not meet the threshold for a small effect size. These findings did not support the hypothesis that higher adherence would be related to a lower proportion of abnormal CRP levels in the year after study participation.

No significant correlations were found between multivitamin adherence and proportion of abnormal ESR levels ($r = .18$, $p > .05$) or between calcium adherence and proportion of abnormal ESR levels ($r = .27$, $p > .05$), yet the correlation between iron adherence and proportion of abnormal ESR levels was meaningful (iron adherence $r = -.48$, $p > .05$). Correlations between multivitamin adherence and proportion of abnormal ESR levels, as well as between calcium adherence and proportion of abnormal ESR levels met the threshold for a small effect size. Correlations between iron adherence and proportion of abnormal ESR levels were found to be medium in effect size. These results only partially supported the hypothesis that with an increased adherence to the three

supplement categories throughout the study, the proportion of abnormal ESR present in the year after the study would decline.

Adherence and Laboratory-Based Nutritional Outcomes

Adherence scores to iron and calcium supplements were used to predict the presence of select nutritional abnormalities in the 12 months after study completion. Nutritional abnormalities included factors indicative of iron deficiency and low total calcium, which were identified by several laboratory indices. Regarding factors indicative of possible iron deficiency, I examined the following hematological indices as outcomes of iron adherence: HGB, RBC, HCT, MCV, and MCH. Correlations were run using the proportion of abnormal laboratory indices during the 12 months after study completion. A meaningful correlation was found between iron adherence and proportion of abnormal iron labs (r = -.34, p > .05). This correlation was found to have a medium effect size. This finding supported the hypothesis that those with higher adherence during study participation would be less likely to have abnormal iron labs 12 months after study participation.

Finally, the relationship between patients' calcium adherence during the study and the proportion of total calcium lab abnormalities during the 12 months after study participation was examined. Results suggested that there was no significant association between calcium adherence during the study and proportion of abnormal calcium lab values in the 12 months after the study (r = -.06, p > .05). This finding did not support the hypothesis that those who have higher calcium supplement adherence during study participation are more likely to have fewer low total calcium labs in the 12 months after study participation.

Growth Improvement

Adherence scores to multivitamin, iron, and calcium supplements during study participation were used to predict the presence of growth improvement in the 12 months following study participation. Correlations were run between adherence and growth improvement (coded as either a presence or absence of growth improvement). It was found that higher adherence to any of the three supplements during the study did not predict growth improvement in the 12 months following the study (multivitamin adherence $r = .04$, $p > .05$; iron adherence $r = .17$, $p > .05$; and calcium adherence $r = .03$, $p > .05$). Since growth improvement may not be expected when disease activity is present, we conducted additional analyses with only those who had no disease activity. In these analyses, no significant relationship was found between increased adherence to any of the three supplements and growth improvement following study participation (multivitamin adherence $r = -.06$, $p > .05$; iron adherence $r = .19$, $p > .05$; and calcium adherence $r = .00$, $p > .05$).

Discussion

The current study was designed to examine rates of adherence to dietary supplements among youth with IBD and also to examine predictors and outcomes of supplement adherence. Rates of supplement adherence were found to be quite low in the present study (32% to 44%). Supplement adherence rates were significantly lower than those of medication adherence rates of the same population (i.e., > 90%); however these rates were comparable to supplement adherence rates found by Kitney et al. (2009). There are many reasons that supplement adherence rates may have been lower than

medication adherence rates. One explanation relates to the importance that families and health providers might place on supplements compared to prescription medications. Children and parents may not consider supplementation to be as important to the child's medical regimen as are their medications. Additionally, health care providers may not be placing a large emphasis on the importance of supplementation. Finally, limited knowledge of the benefits of supplements may interfere with supplement adherence. Families may not know the benefits supplements can provide them in the long term and may not notice any short-term benefits of taking the supplements. We found that children with higher knowledge of the benefits of supplements were more likely to be adherent to the supplements (Figure 1). Many of the prescription medications that children take for IBD are small pills that are easy to swallow. In contrast, children may be more opposed to taking supplements that can sometimes be large, odorous, and cause stomach upset if taken without food. Also, it is possible that families may be opposed to increasing the complexity of their medical regimen by adding supplements and may choose to focus just on prescription medication, viewing the supplements as less important. The large discrepancy between rates of adherence to supplements compared to rates of oral IBD maintenance medication adherence from the same sample, point out the importance of examining supplement adherence separately from oral medication adherence (Table 1).

Although supplement adherence overall was low, several meaningful predictors of supplement adherence were found. Predictors included higher knowledge (for multivitamin, iron, and calcium adherence), high levels of youth and mother involvement (for iron and calcium adherence), and baseline CRP levels (for multivitamin adherence) (Table 2; Table 3; Table 4). Finding knowledge as a predictor of adherence supports the

findings of Alm-Roijer et al. (2004) in which higher knowledge was also found to be a predictor of adherence among coronary artery disease patients. Additionally, finding family involvement as a meaningful predictor of supplement adherence is similar to the findings of Anderson et al. (1990) in which high levels of parent and youth involvement promoted more optimal diabetes management. In previous studies high disease activity has not been shown to predict adherence to oral maintenance medications in IBD (Greenley et al., 2010), although measures used to indicate disease activity in previous studies were physician global assessment ratings, rather than CRP levels. Perhaps associations between CRP levels and multivitamin adherence were found in the current study because CRP levels measure changes intravenously and may predict future disease activity that may not yet be detectable by physicians or patients on the basis of a physical exam or report of current symptoms. Overall, fewer significant predictors were identified than were expected. This may be due to the small sample size or low disease activity in the sample. In addition, the majority of meaningful predictors of adherence were mainly psychosocial in nature. It is possible that because participants tended to have low levels of disease activity and few disease symptoms, it was harder to find relationships between biological factors and adherence than if the sample had had larger rates of disease activity.

Several relationships between adherence and disease-related outcomes were found in the current study. Specifically, higher calcium adherence during the study predicted a greater proportion of abnormal CRP levels during the twelve months following study participation, a finding contrary to prediction. In addition, higher iron adherence during the study was found to predict a lower proportion of abnormal ESR levels in the year

following study participation. Similarly, both higher iron and calcium supplement adherence predicted fewer nutrient-specific lab deficiencies in the twelve months following study participation. Fewer significant outcomes of supplement adherence were identified than were expected. This may be again due to low levels of disease activity and few problems with growth in the overall sample. Therefore, there may have been little room for improvement of disease activity, nutrition status, or growth as a result of better supplement adherence. It is also possible that adherence to supplements alone is not enough to promote better disease-related outcomes. It is possible that the combination of good adherence to the IBD treatment medications and good adherence to supplements might be more important in predicting positive outcomes than supplement adherence alone. Additionally, regarding our measure of growth improvement, participants' parental height was not considered before analyses for growth impairment were conducted. There also was no consideration for participants who have finished puberty and have completed growth.

Limitations

In addition to the limitations mentioned above, there are several other noteworthy limitations that should be acknowledged. Supplement adherence rates were abstracted from a study with alternative goals, rather than from a study that was primarily designed to investigate supplement adherence. Because of this, only self- report measures of supplement adherence were available, rather than more sophisticated measures of adherence or even multiple measures of supplement adherence. In addition, it may have been important to consider each participant's time since diagnosis as a factor. Patients who were enrolled closer to the time of their diagnosis may have more nutritional

deficiencies and more disease activity than patients who were diagnosed a long time ago. This may be due to less time on maintenance medications to get their disease under control. In addition, in this sample, a majority of participants had low levels of disease activity and few nutritional abnormalities overall. Having a more diverse sample with respect to levels of disease activity and malnutrition could help to improve the chances of finding a significant relationship between adherence and these disease factors. Similarly, children who are newly diagnosed may not have had sufficient time to experience catch up growth common in adolescents soon after their disease has been controlled via medication. Newly diagnosed patients who have never had a medical regimen before may also have more difficultly remembering or scheduling taking their medications and supplements compared to those who have been diagnosed for a longer period of time.

Future Research Directions

In the future, a larger sample will allow researchers to get a better understanding of the overarching predictors and outcomes being examined here. A larger sample can maximize probability of finding statistically significant relationships between variables, while limiting the influence of outliers. A larger sample also more accurately reflects the IBD population so it helps the results generalize better. Adherence can also be measured in a more precise and accurate way other than self-report. Self-report in adolescents leaves room for honest miscalculation or over estimation of doses missed. Perhaps the use of a software pill bottle to track particular supplements can be implemented. Changes could also be made to the sample to include only adolescents who have not yet reached the end of puberty. This would allow for growth improvements to be observed in all participants.

Other variables that may be beneficial to examine could include: time since diagnosis, number of medical or emergency visits due to disease, knowledge of nutritional abnormality, knowledge of status of disease activity, body mass index percentile, and results of dual-energy X-ray absorptiometry (DEXA) scans. Having participants who have a greater range of times since diagnosis will aid in determining if this is an important variable in that should be controlled for when examining disease activity and growth improvement. Acquiring documentation of number of medical or emergency visits may be another factor in determining disease severity. High disease activity is often indicated when children have a relapse, sometimes requiring hospitalization or extra clinical visits. If children have knowledge regarding the severity of their disease or knowledge regarding their nutritional abnormality detected via blood draws, they may be more motivated to take their supplements. This might be especially important for supplement adherence, where the purpose of taking the supplement isn't easily observable. Additionally, patients who receive DEXA scans will have greater information regarding their bone density status, which may motivate children to adhere to their calcium supplement specifically. Finally, body mass index percentile can aid in determining an adolescent's malnutrition status, as many children lose weight as a result of malabsorption and a need for higher caloric intake.

Treatment Implications

Since multiple studies, including the current study, have shown that supplement adherence rates in this population are quite low, health professionals should place a larger emphasis on adherence to supplements in the context of the routine outpatient IBD clinic appointments. Medical staff should take time during routine check ups to educate their

patients, especially adolescents, on the supplements suggested to them. It is vital to stress the importance and reasons for adhering to supplements particularly because knowledge has been shown to be a significant predictor of higher adherence. Similarly, because family involvement was shown to be a predictor of higher adherence, parents may also need to be educated on how supplements can aid in improving their child's condition, and how supplements can be beneficial to them overall. In addition, providers can work with families to make sure both parents and youth are very involved in supplement administration as a possible way to improve adherence. One-to-one counseling with a trusted health provider has been shown in several studies including one by Stockwell-Morris & Schulz (1992) to be an effective way to improve adherence.

In conclusion, this study discovered that overall adherence rates to multivitamin, calcium, and iron supplements were quite low for adolescents with IBD, and much lower than rates of oral IBD medication in this same sample. Salient predictors of supplement adherence tended to be psychosocial rather than biological in nature, with knowledge being the most consistent predictor of adherence during study participation. Iron adherence was associated with biological outcomes including lower proportion of abnormal ESR values and fewer iron-related nutrient deficiencies. However, adherence to supplements did not significantly impact growth in the year following study participation. Although this study provides some initial information about supplement adherence, additional research with larger and more diverse samples is needed to more fully understand the importance of supplement adherence in the context of pediatric IBD.

References

Alm-Roijer, C., Stagmo, M., Uden, G., & Erhardt, L. (2004). Better knowledge improves adherence to lifestyle changes and medication in patients with coronary heart disease. *European Journal of Cardiovascular Nursing, 3*, 321-330.

Anderson, B. J., Auslander, W. F., Jung, K. C., Miller, J. P., & Santiago, J. V. (1990). Assessing family sharing of diabetes responsibilities. *Journal of Pediatric Psychology, 15*, 477-492.

Bager, P., Befrits, R., Wikman, O., Lindgren, S., Moum, B., Hjortswang, H., & Dahlerup, J. F. (2011). The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. *Scandinavian Journal of Gastroenterology*, *46*, 304-309.

Centers for Disease Control and Prevention. (2009). Z-score data files. Retrieved from: http://www.cdc.gov/growthcharts/zscore.htm

Crohn's and Colitis Foundation of America. (2013). Living with Crohn's disease. Retrieved from: http://www.ccfa.org/resources/living-with-crohns-disease.html

Crohn's and Colitis Foundation of America. (2013). Living with ulcerative colitis. Retrieved from: http://www.ccfa.org/resources/living-ulcerative-colitis.html

Eiden, K. A. (2003). Nutritional considerations in inflammatory bowel disease. *Practical Gastroenterology*, *5*, 33-54.

Gore, R. M., Balthazar, E. J., Ghahremani, G. G., & Miller, F. H. (1996). CT features of ulcerative colitis and Crohn's disease. *American Journal of Roentgenology*, *167*, 3-15.

Greenley, R. N., Doughty, A., Stephens, M., & Kugathasan, S. (2010). Development of the IBD family responsibility questionnaire. *Journal of Pediatric Psychology, 35,* 183-187.

Greenley, R. N., Kunz, J. H., Biank, V., Martinez, A., Miranda, A., Noe, . . . Stephens, M. C. (2012). Identifying youth nonadherence in clinical settings: Data-based recommendations for children and adolescents with inflammatory bowel disease. *Inflammatory Bowel Disease, 18*, 1254-1259.

Greenley, R. N., Stephens, M., Doughty, A., Raboin, T., & Kugathasan, S. (2010). Barriers to adherence among adolescents with inflammatory bowel disease. *Inflammatory Bowel Disease*, *16*, 36-41.

Guindi, M. & Riddell, R. H. (2004). Indeterminate colitis. *Journal of Clinical Pathology, 57*, 1233-1244.

Gurram, B., Joeckel, R., & Stephens, M. (2012). Nutrition in pediatric inflammatory bowel disease. *Practical Gastroenterology*, *104*, 56-62.

Hommel, K. A. & Baldassano, R. N. (2010). Brief report: Barriers to treatment adherence in pediatric inflammatory bowel disease. *Journal of Pediatric Psychology*, *35*, 1005-1010.

Hommel, K. A., Denson, L. A., Crandall, W. V., & Mackner, L. M. (2008). Behavioral functioning and treatment adherence in pediatric inflammatory bowel disease: Review and recommendations for practice. *Gastroenterology & Hepatology*, *4*, 785-791.

Hommel, K. A., Greenley, R. N., Herzer, M., Gray, W. N., & Mackner, M. L. (2013). *Self-aanagement in pediatric inflammatory bowel disease: A clinical report of the*

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Manuscript submitted for publication.

Husain, T. M. & Kim, D. H. (2002). C-reactive protein and erythrocyte sedimentation rate in orthopedics. *The University of Pennsylvania Orthopedic Journal, 15*, 13-16.

Hyams, J. S., Ferry G. D., Mandel, F. S., Gryboski, J. D., Kibort, P. M., Kirschner, B. S., . . . Boyle, J. T. (1991). Development and validation of a pediatric Crohn's disease activity index. *Journal of Pediatric Gastroenterology and Nutrition, 12*, 439-447.

IBM SPSS Statistics [Computer software]. (17.0). Armonk, NY: IBM.

Ingerski, L. M., Baldassano, R. N., Denson, L. A., & Hommel, K. A. (2010). Barrier to oral medication adherence for adolescents with inflammatory bowel disease, *Journal of Pediatric Psychology, 35*, 683-691.

Kappelman, M. D., Moore, K. R., Allen, J. K., Cook, S. F. (2012). Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Digestive Diseases and Sciences, 58*, 519-522.

Kitney, L., Turner, J. M., Spady, D., Malick, B., El-Matary, W., Persad, R., & Huynj, H. Q. (2009). Predictors of medication adherence in pediatric inflammatory bowel disease patients at the Stollery Children's Hospital. *Canadian Journal of Gastroenterology*, *23*, 811-815.

Laihai, J. K., Koskinen, J. O., Waris, M. E., & Jansen, C. T. (2005). Adaptation of the human skin by chronic solar-simulating UV irradiation prevents ultraviolet-b irradiation-induced rise in serum C-reactive protein levels. *American Society for Photobiology*, *81*, 654-658.

Lok, K. H., Ng, C. H., Hung, H. G., Li, K. F., Li, K. K., & Szeto, M. L. (2008). Correlation of serum biomarkers with clinical severity and mucosal inflammation in Chinese ulcerative colitis patients. *Journal of Digestive Diseases*, *9*, 219-224.

Mamula, P., Markowitz, J. E., Baldassano, R. N., (2008). Pediatric inflammatory bowel disease. New York, NY: Springer.

McQuaid, E. L., Kopel, S. J., Klein, R. B., & Fritz, G. K. (2003). Medication adherence in pediatric asthma: Reasoning, responsibility, and behavior. *Journal of Pediatric Psychology, 28*, 323-333.

Moeeni, V. & Day, A. S. (2011). Impact of inflammatory bowel disease upon growth in children and adolescents. *ISRN Pediatrics*, 1-5.

Munoz, M., Gomez-Ramirez, S., & Garcia-Erce, J. A. (2009). Intravenous iron in inflammatory bowel disease. *World Journal of Gastroenterology, 15*. 4666-4674.

Newby, E. A., Sawczenko, A., Thomas, A. G., & Wilson, D. (2008). Interventions for growth failure in childhood Crohn's disease. *The Cochrane Database of Systematic Reviews, 3*, 1-15.

Paerregaard, A. & Uldall-Urne, F. (2005). Anthropometry at the time of diagnosis in diagnosis in Danish children with inflammatory bowel disease. *Acta Paediatrica, International Journal of Pediatrics*, *94*, 1682-1683.

Peterlik, M. & Cross, H. S. (2005). Vitamin D and calcium deficits predispose for multiple chronic diseases. *European Journal of Clinical Investigation, 35*, 290-304.

Quittner, A. L., Modi, A. C., Lemanek, K., Landis, C., & Rapoff, M. (2008). Evidence-based assessment of adherence to medical treatments in pediatric psychology. *Journal of Pediatric Psychology*, *33*, 916-936.

Rapoff, M. A. (2010). *Adherence to pediatric medical regimens*. Kansas City, KS: Springer.

Rees, D. C. & Gibson, J. S. (2012). Biomarkers in sickle cell disease. *British Journal of Haematology*, *156*, 433-445.

Sewitch, M. J., Abrahamowicz, M., Barkun, A., Bitton, A., Wild, G. E., Cohen, A., Dobkin, P. L. (2003). Patient nonadherence to medication in inflammatory bowel disease. *The American Journal of Gastroenterology, 98*, 1535-1544.

Stockwell-Morris, L. & Schulz, R.M. (1992). Patient compliance – an overview. *Journal of Clinical Pharmacy and Therapeutics*, *17,* 283-295.

Strople, J. & Gold, B. D. (2008). Laboratory evaluation of pediatric inflammatory bowel disease. In P. Mamula, J. E. Markowitz, & R. N. Baldassano (Eds.), Pediatric inflammatory bowel disease (pp. 179-191). New York, NY: Springer.

Sturniolo, G. C., Di Leo, V., Ferronato, A., D'Odorico, A., & D'Inca, R. (2000). Zinc supplementation tightens "leaky gut" in Crohn's disease. *Inflammatory Bowel Disease*, *7*, 94-98.

Thayu, M., Semeao, E., & Leonard, M. B. (2008). Bone health assessment in pediatric inflammatory bowel disease. In P. Mamula, J. E. Markowitz, & R. N. Baldassano (Eds.), Pediatric inflammatory bowel disease (pp. 275-294). New York, NY: Springer.

Vasseur, F., Gower-Rousseau, C., Vernier-Massouille, G., Dupas, J. L., Merle, V., Merlin, B., . . . Turck, D. (2010). Nutritional status and growth in pediatric Crohn's disease: A population-based study. *The American Journal of Gastroenterology, 105*, 1893-1900.

Vermeire, S., Van Assche, G., & Rutgeerts, P. (2006). Laboratory marker in IBD: Useful, magic, or unnecessary toys? *An International Journal of Gastroenterology and Hepatology*, *55*, 426-431.

Walders, N., Drotar, D., & Kercsmar, C. (2000). The allocation of family responsibility for asthma management tasks in African-American adolescents. *Journal of Asthma*, *37*, 89-99.

Walters, T. D. & Griffiths, A. M. (2008). Growth impairment in pediatric inflammatory bowel disease. In P. Mamula, J. E. Markowitz, & R. N. Baldassano (Eds.), Pediatric inflammatory bowel disease (pp. 103-117). New York, NY: Springer.

Zelikovsky, N. & Schast, A. P. (2008). Eliciting accurate reports of adherence in a clinical interview: Development of the medical adherence measure. *Pediatric Nursing*, *34*, 141-146.

Zemel, B. (2008). Assessment of growth and nutritional status in pediatric inflammatory bowel disease. In P. Mamula, J. E. Markowitz, & R. N. Baldassano (Eds.), Pediatric inflammatory bowel disease (pp. 295-306). New York, NY: Springer.