THE IMPACT OF VITAMIN D ON DISEASE ACTIVITY IN CROHN'S DISEASE

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ABSTRACT

Canada has the highest rate of Inflammatory Bowel Disease (IBD) in the world with approximately 0.67%. One of the primary nutritional health issues faced by Crohn's disease (CD) patients is vitamin D deficiency, which can subsequently lead to more serious health complications. Vitamin D is shown to act as a modulator for the autoimmune system among CD patients.

Phase I study aimed to determine vitamin D concentrations and disease activity among CD cases in Canada and Saudi Arabia, and evaluate the impact of higher doses of vitamin D compared to EAR on disease activity among CD patients. This pilot study was a double blind, randomized, control trial involving approximately 60 recent, active CD patients engaged in induction therapy. The sample size includes patients in Saskatoon, Saskatchewan, Canada (n=30) and Riyadh, Saudi Arabia (n=30). The patients have been divided into three groups to receive different oral doses of vitamin D including: 1: 400 IU/day (Control group, EAR level) 2: 2,000 IU/day 3: 10,000 IU/day. Data were collected at baseline (0), end of 9 weeks (end of intervention), and at 2 months follow-up. Along with anthropometric measurements participants undergo laboratory examinations such as, WBC, HGB, Hct, platelets, ferritin, vitamin D, hsCRP and calprotection, undertake the Health related quality of life (HRQOL), and fill out socio-demographic and physical activity questionnaires. We also assessed their dietary intake at the baseline and Week 9 using two sets of three 24-hour dietary recalls. Due to a small sample size (n=9 cases) we have recruited, we presented Phase I as a case series.

Phase II study determined the association between vitamin D concentrations and disease activity among CD cohort in Saskatoon, Canada. In a retrospective cohort design, we studied 201 CD patients; 116 participants had vitamin D data. We extracted data from medical records over three years at IBD clinic, Royal University Hospital, Saskatoon, Canada. I evaluated the association between vitamin D status (serum 25OHD) and indicator of disease activity (hsCRP) as well as Harvey-Bradshaw index (HBI) in CD patients. The analyses conducted in the presence of other potential factors in three-time points (baseline, midpoint, last visit) using generalized estimating equation (GEE).

Vitamin D concentrations was improved significantly from baseline to the last visit ($p=0.005$). At the baseline, mean 25OHD was 58.2±30.0 nmol/L; 26% of patients had optimal, 30% had adequate, 26% had insufficient, and 18% patients had deficient vitamin D levels. At the midpoint, mean serum vitamin D concentrations was 60.1±31.2 nmol/L; 31.3% had optimal level, 31,3% patients had insufficient level, 22.1% patients had adequate level, and 15.2% patients were vitamin D deficient. At final visit, mean vitamin D was 74.5±42.6 nmol/L; 43.9% patients had optimal and 24.2% patients had adequate levels of vitamin D, while 18.1% patients were vitamin D insufficient and 13.6% patients had vitamin D deficiency. Vitamin D concentrations showed significant inverse association with hsCRP level over 15 months. Compared to vitamin D deficient category, patients in other categories (including insufficient, adequate and optimal levels of vitamin) had significantly lower hsCRP level over time ($p <0.05$).

Vitamin D deficiency was associated with higher disease activity in Crohn's disease patients. Higher vitamin D (25OHD) concentrations was associated with lower D disease activity levels in Crohn's patients over 15 months.

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LIST OF ABBREVIATIONS

Abb	Description	Abb	Description
AST	Aspartate aminotransferase	IL	Interleukin
ALT	Alanine transaminase	IOM	Institute of medicine
BMD	Bone mineral density	IUs	International Units
BMI	Body mass index	Mcgs	Micrograms
CBC	Complete blood count	MRI	Magnetic resonance imaging
CCFC	Crohn's and Colitis Foundation of Canada	MET	Metabolic equivalent value
CCHS	Canadian Community Health Survey	MS	Multiple sclerosis
Ca	Calcium	Na	Sodium
CD	Crohn's disease	OR	Odds ratio
CDAI	Crohn's disease activity index	PTH	Parathyroid hormone
CHMS	Canadian Health Measures Survey	PAI	Physical activity index
CRP	C-reactive protein	PCDAI	Pediatric Crohn's Disease Activity Index
CT	X-ray computed tomography	RXR	Retinoid X receptor
DBP	Vitamin D-binding protein	RDA	Recommended Dietary Allowance
DCs	Dendritic cells	SIBDQ	Short IBD questionnaire
DRIs	Dietary Reference Intakes	SBE	Small Bowel Enteroclysis
EAR	Estimated Average Requirements	SZA	Solar zenith angle
ESR	Erythrocyte sedimentation rate	Sat/Unsat	Saturated /unsaturated fat
EE	Energy expenditure	TNF	Tumor necrosis factors
ECG	Electrocardiography	T_h	T helper cell
FNB	The Food and Nutrition Board	UC	Ulcerative colitis
Fe	Iron	UL	Tolerable Upper Intake Level
GEE	Generalized estimating equation	USDA	United State Department of Agriculture
HEI	Healthy Eating Index	UV	Ultraviolet radiation
HBI	Harvey-Bradshaw index	VDR	Vitamin D receptor
Hs-CRP	High sensitivity CRP	VDRE	Vitamin D receptor elements
HRQOL	Health-related quality of life	Vit	Vitamin
IBD	Inflammatory bowel disease	WCC	White blood cell count
IBDQ	Inflammatory bowel disease questionnaire	WHO	World Health Organization

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CHAPTER 1

1. INTRODUCTION

1.1 Rationale

The prevalence of autoimmune diseases is rapidly increasing around the globe (Economou & Pappas, 2008). Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are among the fastest growing autoimmune diseases in developing and developed countries (Economou & Pappas, 2008). Canada has one of the highest rates of IBD in the world (0.67% of Canadian population), and Saudi Arabia, a developing country, is facing an increasing number of incidents every year (Benchimol et al., 2009; Fadda et al., 2012). The role of nutrition in preventing disease activity in IBD, as well as the impact of IBD on the nutritional health of patients, has been documented in recent literature (Cantorna, 2006; Graham & Kandil, 2002; Kamen & Tangpricha, 2010). In addition to its many health benefits, vitamin D has an impact on the modulation of the autoimmune system by development and function T cells (Cantorna, 2006). However, vitamin D insufficiency is a pandemic in seemingly healthy people, particularly those diagnosed with IBD (Holick & Chen, 2008; Langlois, Greene-Finestone, Little, Hidiroglou, & Whiting, 2010). One of the primary nutritional health issues faced by patients with CD is vitamin D deficiency (25(OH)D <20 ng/ml), which can lead to more serious health complications such as increasing disease activity (Joseph, George, Pulimood, Seshadri, & Chacko, 2009; Narula & Marshall, 2012). Studies suggest that vitamin D supplements are beneficial in treating CD because higher levels of vitamin D supplementation can significantly decrease disease activity (Ananthakrishnan et al., 2012). Jorgensen et al. (2010) stated that a daily vitamin D_3 supplement of 1200 IU/d will significantly increase serum vitamin

D and therefore will decrease the risk of disease activity in cases of CD. However, the optimal dose by which disease activity can be controlled is not well known.

The purpose of this study is to evaluate the impact of vitamin D supplementation on the disease activity among CD cases in Canada and Saudi Arabia. Many gaps exist in the literature on this topic. The majority of studies have focused on providing normal (600 IU) or high doses of vitamin D supplements (up to 5000 IU) to patients with CD. To our knowledge, only one unpublished study has been conducted in the United States to determine the effect of high doses (1,000 and 10,000 IU/ d) of vitamin D on CD. Only a few published studies measured vitamin D levels in patients with CD in Canada (Leslie, Miller, Rogala, & Bernstein, 2008a). However, thus far there has been no clinical trial in Saudi Arabia that explores the relationship between CD and a high dose of vitamin D supplements.

In a pilot clinical trial (Phase I), we planned to evaluate the impact of different doses of vitamin D (400, 2000, 10,000 IU) on disease activity. We collected data on nutritional status and assess other factors that may have an impact on disease activity, including physical activity and socio-economic status. Similar research was completed by Dustin Boothe at Weill-Cornell Medical College in the United States, and he presented it at the American College of Gastroenterology (ACG) Annual Scientific Meeting 2011. However, there remains a need for research in this area to evaluate the effect of high doses of vitamin D supplementation in populations with different ethnic backgrounds and in other geographic areas with diverse environmental factors.

In a retrospective cohort (Phase II) study, we aimed to determine the association between vitamin D status and disease activity among CD cohort in Saskatoon, Canada. We evaluated the association between vitamin D status (serum 25OHD) and indicator of disease activity (hsCRP) as well as Harvey-Bradshaw index (HBI) in CD patients. Different study designs were conducted

to examine the association between vitamin D status, disease activity and other predictors. However, we conducted this study to address the research question.

1.2 Study Objective

1.2.1 Study phase I (Clinical trial) objective: to determine the effect of vitamin D supplementation on disease activity in patients with Crohn's disease in Canada and Saudi Arabia.

Specific objective and hypothesis 1.

Objective 1. To determine vitamin D levels and disease activity in cases of Crohn's disease in Canada and Saudi Arabia.

Hypothesis 1: Patients who are suffering from Crohn's disease are at risk of vitamin D deficiency / insufficiency.

Specific objective and hypothesis 2.

Objective 2**.** To evaluate the impact of vitamin D in doses higher than the Recommended Dietary Allowance (RDA) (>600 IU) on disease activity in patients with Crohn's disease

Hypothesis 2: Providing vitamin D in doses higher than the RDA reduces disease activity in cases of Crohn's disease.

1.2.2 Study Phase II (Retrospective cohort) objective: To determine the association between vitamin D concentrations and disease activity in a cohort of patients with CD over three years.

1.3 Significance

The majority of studies regarding Crohn's disease and vitamin D are focused on normal doses of vitamin D supplementation. To our knowledge, there is only one unpublished study that investigates the effect of a high dose of vitamin D (10,000 IU) on CD (Boothe, Lakehomer, Jacob, Scherl, & Bosworth, 2011). Another study focused on the effect of 5000 IU/d of vitamin D_3 supplementation on disease activity in CD (Yang et al., 2013a). It is therefore imperative to

investigate how high doses of vitamin D supplementation affect disease activity in patients with Crohn's disease. In addition, the association of vitamin D concentration and disease activity in CD patients who were taking vitamin D supplements in natural setting. The results from this study will be beneficial to patients and researchers by contributing to their understanding of the role of vitamin D supplementation in disease activity in patients with CD.

CHAPTER 2

2. LITERATURE REVIEW

2.1 Crohn's Disease

2.1.1 Introduction to IBDs

Dr. Burrill Bernard Crohn and his two colleagues, Dr. Gordon Oppenheimer and Dr. Leon Ginzburg, discovered Crohn's disease in 1932 (Crohn, Ginzburg, & Oppenheimer, 1952). Inflammatory bowel diseases (IBDs) are diseases that refer to two distinct disorders: Crohn's disease (CD) and ulcerative colitis (UC). These diseases are characterized by chronic inflammation and idiopathic relapsing disorders (Frank et al., 2007). Although the symptoms can be quite similar, the areas affected in the digestive tract are different (Nabalamba, Bernstein, & Seko, 2004). Ulcerative colitis affects the rectum and colon (lining of the large intestine), whereas Crohn's disease affects the digestive tract from the mouth, which is the beginning of the digestive tract, to the terminal ileum (all the layers of the small intestine) or the colon, or both. Ulcerative colitis and Crohn's disease can cause ulceration, which is often present in serious cases of these diseases. Additionally, inflammation (redness and swelling) occurs in the intestine; whereas CD occurs in patches of healthy tissue that can then expand into the intestinal wall (CCFC, 2008, 2012; Cohen, 1995; Head, Jurenka, & Ascp, 2004; Nabalamba et al., 2004). These diseases occur in people of any age; CD usually begins in youths and young adults between the ages of 15 and 35. Instances of UC increase at ages 15–30 and then at ages 50–70, with 25% of cases starting in childhood before the age of 18 (CCFC, 2012; Nabalamba et al., 2004; Sands and Siegel 2010).

2.1.2 Epidemiology of IBDs in Canada and Saudi Arabia

A number of epidemiological studies discuss the prevalence and incidence of IBDs in the world. Worldwide, there are fewer than one to 15 new incidences of CD per 100,000 persons yearly; whereas the incidence of ulcerative colitis (UC) ranges from two to more than 20 per 100,000 persons yearly (Herrinton et al., 2007; Loftus et al., 2007). The disease prevalence has increased dramatically in the developed countries of Northern Europe and North America (Loftus et al., 2007). The highest incidence rates of IBD are in Canada (UC: 248 per 100,000 persons; CD: 319 per 100,000 persons) and Europe (322 per 100,000 persons for CD in Italy; 505 per 100,000 persons for UC in Norway; Bengtson et al., 2009; Bernstein et al., 2006; Cottone et al., 2006).

According to a 2008 report from the Crohn's and Colitis Foundation of Canada, Canada has the highest rate of IBD in the world. The greatest estimate of the prevalence of IBDs in 2012 was approximately 0.67% of the Canadian population; in other words, there were 233,000 patients with IBD (129,000 with CD and 104,000 with UC) in Canada (CCFC, 2008, 2012). In 1998–2000, there were 16.3 new incidences of CD and 12.9 of UC per 100,000 patients in Canada. New cases of IBDs are likely to reach 10,200 every year, with 5,700 cases having CD and 4,500 with UC. There are more diagnosed cases of CD than UC in Canada. Across Canada, Ontario has the highest provincial estimate rate of IBD, with approximately 55,000 per 100,000 Canadians living with CD and 40,200 Canadians with UC. The province with the second highest estimate rate in Canada is Quebec, with a rate of 20,900 of CD and 20,500 per 100,000 with UC in 2012. The prevalence in Saskatchewan is approximately 5,000 per 100,000 living with CD and 4,000 with UC (CCFC, 2012). In the United States, only two epidemiological studies have been conducted: one in California and one in Minnesota. The incidence of CD was between six and

eight per 100,000 cases, with a prevalence of UC between nine and 12 per 100,000 cases (Herrinton et al., 2007; C. Loftus et al., 2007).

The prevalence of IBDs in Saudi Arabia has increased over the years. Fadda et al. (2012) conducted a retrospective study in Riyadh, the capital city of Saudi Arabia, from 1970 to 2008 in which researchers collected data from 312 patients with IBDs. The researchers found a significant increase in the number of incidences of CD and UC in the last 10 years when comparing 1970 to 1990. The study found 63% of participants with CD and 37% with UC; 48.7% were men and 51.3% were women. The majority of cases (56%) occurred in the central region (167 out of 312 patients). The researchers concluded that there was a gradual increase in the incidence of IBDs in Saudi Arabia throughout the years of the study. Another study demonstrated an increase in the number of CD cases (77 CD cases) at King Khalid University Hospital in Riyadh, Saudi Arabia, from 1994 to 2004 (Al-ghamdi et al., 2004). Aljebreen et al. (2014) recently studied the clinical epidemiology and phenotypic characteristics of CD in Riyadh, Saudi Arabia, among 497 CD patients from 2009 to 2013. The study showed that the majority of the patients are men (58.6%)—young adults between 15 to 30 years of age. According to the Montréal classification, most CD patients (48.8%) had ileocolonic involvement, 43.5% had involvement in terminal ileum, and 7.7% had colon involvement (Aljebreen et al., 2014). Some possible reasons for this increase include diet, environmental factors, and modernization (Fadda et al., 2012; Goh & Xiao, 2009).

2.1.3 Clinical Presentation of CD

Signs and symptoms of CD depend on the location of the disease. It is difficult to diagnose CD in the beginning, and it usually takes 3 years to confirm that the disease is present. In general, gastrointestinal symptoms include persistent diarrhea (loose, watery), abdominal cramps and pain (in the right lower quadrant), rectal bleeding, constipation, incomplete

evacuation, and stomatitis are more common in CD. Some patients may also experience perianal fistula, which can cause pain and bleeding. Other common symptoms found in CD patients include fever (in more than 50% of patients), fatigue, loss of appetite, and arthritis. Many patients have nutritional deficiency and malabsorption of nutrients, leading to more than 80% of CD patients experiencing weight loss (CCFC, 2008; DiPiro et al., 2005; Herfindal & Gourley, 2003). In addition, intestinal obstruction is a common complication that increases the risk of small intestine and colon cancer in CD patients (CCFC, 2008). The symptoms correlate well with the severity of the disease activity (CCFA, 2014d; Sands, 2010). Table 2.1 presents Clinical Features of Crohn's Disease. Table 2.2 Types of Crohn's Disease with Associated Symptoms.

Table 2.1 Clinical Features of Crohn's Disease

Clinical features	**Signs and Symptoms**
Common symptoms	Abdominal pain, diarrhea, fever, fatigue, anorexia, weight loss, rectal bleeding, nausea
Common clinical signs	Palpable mass in the right lower quarter, abdominal tenderness, guaiac positive stool
Common laboratory and radiographic finding	Mild leukocytosis and anemia, elevated ESR or CRP, strictures, fistulas, small involvement
Extra-intestinal magnification	a) 25 % Joint manifestations (arthralgia- arthritis) b) 15 % Mucocutaneous manifestations (erythema nodosum- aphthous ulcers of mouth-pyoderma gangrenosum). c) 5 % Ocular manifestations (recurrent iritis-episcleritis- uveitis).

Note. Adapted from Inflammatory Bowel Disease translating basic science into clinical practice: Crohn's disease clinical course and complication, (p. 228-244), by Sands Bruce, 2010, West Sussex, UK : Wiley-Blackwell.

Table 2.2 Types of Crohn's Disease with Associated Symptoms

Type of CD	Ileocolitis	Ileitis	Gastroduodenal CD	Jejunoileitis	Crohn's colitis
Area affected	Ileum Colon	Ileum	Stomach The duodenum (beginning of the small intestine)	Jejunum	Colon
Symptoms	Diarrhea, Cramping in the right middle or lower part of the abdomen, weight loss <u>In sever ileitis cases:</u> fistulas or abscess in the lower right of abdomen.		Loss of appetite Weight loss Nausea Vomiting	Pain and cramps after meals Diarrhea Fistulas (in severe cases)	Diarrhea Abscess Fistulas ulcers around the anus Rectal bleeding Skin lesions Joint pains

Note. Adapted from "Types of Crohn's Disease with Associated Symptoms," by Crohn's and Colitis foundation of America, accessed in 2014.

2.1.4 Etiology and Pathogenesis

The exact cause of Crohn's disease is unknown, but scientists have demonstrated that it may be caused by genetic, immunologic, infectious, or environmental factors (Pavli, Cavanaugh, & Grimm, 1996). To date, no evidence has been suggested to demonstrate the contributing factors with the risk of developing CD (UNC, 2014). CD has several gene components in its etiology. The most important genes that significantly increase an individual's risk of developing CD are susceptibility mutations gene NOD2/ CARD15, which is located on chromosome 16 (Hampe et al., 2001; Ogura et al., 2001). The exact mechanism of this gene is unclear, but gene

changes (mutations) disrupt the mucosa of the intestine so that the immune system is then influenced by the bacterial milieu in the digestive tract (Hisamatsu et al., 2003; Ogura et al., 2001; Rosenstiel et al., 2003). The changes appear in approximately 20% of CD cases; however, 4% of the people did not develop CD. In such cases, this gene requires action of unidentified factors such as viruses, bacteria, food additives, nutritional behavior, a weakened immune system, or an intestinal barrier to develop the disease (UNC, 2014). Incidence does increase in the relatives of persons who suffer from IBDs; around 5% to 20% of the people who have CD have at least one family member suffering from the disease. The risk of developing CD increases 30 times when a parents and a siblings have the disease, and 50% of identical twins (Halfvarson, Bodin, Tysk, Lindberg, & Järnerot, 2003; Loftus et al., 2007; Loftus, 2004; Orholm, Binder, Sørensen, Rasmussen, & Kyvik, 2000; Russell & Satsangi, 2008). In addition, Ashkenazi Jewish populations and those of Caucasian origin are more likely to have IBD because of genetic factors (Herrinton et al., 2007).

The prevailing view on inflammation and immune response is that these diseases reflect a primary T cell immune disorder. Another theory has suggested that CD is affected by the distribution of innate immunity (Marks & Segal, 2008). Imbalanced cytokine secretion also works to impair innate immunity, and the response of a sustained microbial resulting in inflammation in the colon can be due to its high bacterial load (Dessein, Chamaillard, & Danese, 2008; Marks et al., 2006). Other causes that may contribute to CD are microorganisms such as *Mycobacterium avium* subspecies *paratuberculosis* (Eckburg & Relman, 2007). Current research has suggested that microorganisms might contribute to reduce the mucus layer and thus its inability to eliminate bacteria in the intestinal walls (Sartor, 2006).

Environmental factors may also contribute to Crohn's disease, such as from a substance that an individual has eaten or microbes that are affected by the virus or the bacteria. Children who have been less exposed to infections in modern environments have high hygiene levels that contribute to the risk of CD (Koloski, Bret, & Radford-Smith, 2008). The disease is more likely to develop in Western industrialized nations than in other regions of the world (UNC, 2014). Smokers are more likely to develop the disease than people who do not smoke. In contrast, the risk of developing UC is lower in smokers than people who do not smoke. Researchers do not know how smoking affect CD, however there is a theory, smoking may cause change in the immune system lead to inflammation (Bernstein et al., 2006; Calkins, 1989; CCUK, 2014). Some studies have demonstrated that there is a correlation between a child's exposure to secondhand smoke and an increased risk of CD (Lashner, Shaheen, Hanauer, & Kirschner, 1993; Mahid, Minor, Stromberg, & Galandiuk, 2007; Persson, Ahlbom, & Hellers, 1990). Furthermore, the etiology of nutrition-related disease may contribute positively to developing CD. Positive associations have been reported between the increase of animal protein, omega-6, and milk protein intakes and an increased risk of developing CD (Hou, Abraham, & El-Serag, 2011; Shoda, Matsueda, Yamato, & Umeda, 1996).

2.1.5 Diagnostic Evaluation in CD

Diagnosis of Crohn's disease is often challenging, It is primarily based on medical history and physical examination and supported by a combination of laboratory, radiographic, and endoscopic tests (Baumgart & Sandborn, 2012; Joseph et al., 2009; Pimentel et al., 2000). Diagnostic tests for CD provide accurate evidence to confirm the disease is present and to rule out other gastrointestinal conditions.

Laboratory examinations, diagnostic imaging and endoscopic examination are critical for exploring the involvement extension and lesion type via colonoscopy, barium enema, and a

small-bowel series (Lashner, 2013). Crohn's disease cannot be diagnosed through blood tests. To monitor the disease activity, routine laboratory investigations should include a complete blood count (CBC), blood chemistry (e.g., electrolytes, albumin, and liver enzymes), inflammatory markers (erythrocyte sedimentation rate [ESR]), C-reactive protein (CRP), and IgG/IgA antibody levels (Jørgensen et al., 2010; Miheller et al., 2009; Shafran et al., 2002). Liver function tests are used to determine liver problems. In addition, electrolytes panel are used to determine potassium levels; lower than normal levels (hypokalemia) occur when diarrhea is present. A stool test (e.g., calprotectin) is a useful tool for predicting a relapse (CCFA, 2014a). C-reactive protein and calprotectin are considered the best biomarkers and correlate well with endoscopic, radiologic, and clinical measurements (Loftus et al., 2007).

Endoscopy is indicated for all CD patients; biopsy specimens are recommended to be taken from different parts of the GI tract to improve diagnostic accuracy (Laass, Roggenbuck, & Conrad, 2014). There are several types of endoscopy (e.g., sigmoidoscopy, colonoscopy, EGD, and capsule endoscopy) that may be utilized based on which part of the GI track needs to be examined (CCFA, 2014a). Doctors use imaging techniques to diagnose CD. One of the most frequently used techniques is small bowel enteroclysis (SBE) (Benevento et al., 2010). Computerized tomography (CT) and magnetic resonance imaging (MRI) scans are helpful to detect signs and complications in the small bowel (e.g., abscesses, intestinal blockages, and fistulas; Rajesh & Maglinte, 2006; Zissin, Hertz, Osadchy, Novis, & Gayer, 2009).

2.1.6 Measurements of Disease Activity in CD

2.1.6.1 Biomarker indicators

C-reactive protein (CRP). C-reactive protein (CRP) is an acute-phase protein that functions in the innate immune system; it is one of the most important proteins produced by the liver at the site of inflammation. CRP levels increase rapidly upon stimulation by TNF-a, IL-1-b,

and IL-6 (Vermeire, Assche, & Rutgeerts, 2004). Crohn's disease is associated with extremely high levels of CRP; however, UC has a moderate-to-absent level. CRP levels correlate well with disease activity; severe CD has higher CRP than does moderate CD, which is higher than mild disease (Vermeire et al., 2004). This protein can be measured through a blood sample and a high sensitivity CRP test assay (Clyne, 1999; Pepys & Hirschfield, 2003; Ridker & Libby, 2007).

Fecal calprotectin. Calprotectin is a calcium and zinc binding protein present in neutrophils' cytosol, where it accounts for 60% of the total cytosol proteins. Fecal calprotectin is strongly correlated with several conditions, including CD and colonic cancer, and the use of nonsteroidal anti-inflammatory drugs (NSAID; Chen, Huang, Chang, & Kong, 2012; Costa et al., 2003; Joshi, Lewis, Creanor, & Ayling, 2010; Tibble et al., 2000). Calprotectin levels may be high in those newly diagnosed with IBD; a moderate concentration indicates inflammation is present or that the disease is becoming worse, whereas a low level excludes IBD (Lab test online, 2013). The test is analyzed using the calprotectin ELISA test (Lab test online, 2013). ALPCO's (2013) calprotectin ELISA assay is used to determine the quantity of human calprotectin in a stool sample. This assay includes two ranges, standard dynamic range (10–600 µg/g or 0.01-0.6 mg), which is the optimal range, and extended dynamic range (30–1,800 µg/g or 0.03-1.8 mg), which is a marker to check the disease activity and mucosal inflammation in IBD patients (ALPCO, 2013).

2.1.6.2 Subjective assessment

Crohn's disease activity index (CDAI). The Crohn's disease activity index (CDAI) is the most widely tool used to measure disease severity and activity in adults. Investigators from the Illinois Midwest Regional Health Center in the United States developed the index in the 1970s. This index has a long history of use and is considered as the gold standard. This index consists of eight clinical variables, including general well-being, abdominal pain and mass, number of liquid

stools, opiates for diarrhea, and presence of complications. A weighting factor is adjusted before each factor is summed (Best, Becktel, Singleton, & Kern, 1976). The three variables, which include number of liquid stools, abdominal pain, and general well-being, are based on a patient's diary for 7 days. A patient with a score of more than 450 points is associated with severe disease, and a score from 220 to 450 indicates moderate disease. Mild disease and response have scores from 150 to 220 and greater than 70 points, respectively; less than 150 points indicates a remission (Best et al., 1976; Hyams et al., 1991; Joseph et al., 2009; Miheller et al., 2009). Modigliani et al. (1989) demonstrated that CDAI is not associated with the extent and severity of ileocolonic CD inflammation. To illustrate, a patient might be in remission with a score of less than 150; however, the endoscopy might show significant colonic inflammation (Modigliani et al., 1990). Table 2.3 presents Crohn's Disease Activity Index.

Pediatric Crohn's disease activity index (PCDAI) is used to assess the disease activity in children. This index measures the same variables used in CDAI. The score ranges from 0 to 100; a score greater than 30 points defines a moderate to severe disease, scores between 11–30 define a mild disease, and a score less than 10 defines a disease that is in remission (Hyams et al., 1991).

Table 2.3 Crohn's Disease Activity Index (CDAI)

Variable	Score	Descriptor	Factors
Liquid stools		Sum of 7 days	Sum × 2
Abdominal pain	None = 0 Mild = 1 Moderate =2 Severe =3	Sum of 7 days	Sum × 5
General well being	Well = 0 Slightly under par =1 Poor =2 Very poor =3 Terrible = 4	Sum of 7 days	Sum ×7
Extra-intestinal	Arthritis/arthralgia, Iritis/uveitis, erythema nodusum, pyoderma, gangrenosum, aphthous stomatitis, anal fistula/ fistula/ abscess, fever > 37.8°C	Number of listed complication	Sum × 20
Antidiarrheal	No= 0 Yes = 1	Use in previous 7 days	Sum ×30
Abdominal mass	No = 0 Questionable = 1 Definite = 5		Sum × 10
Hematocrit	For males, (47 – observed) For females (42 – observed)	Expected - observed	Sum × 6
Weight	Current body weight (kg) standard body weight (kg)	100 x (1 - (current/standard))	

Note. Adopted from "Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study" by Best, et al., 1976, Gastroenterology, 70(3):439-44.

Table 2.4 Pediatric Crohn's Disease Activity Index (PCDAI)

Variable	**Score**
History over 1 week	
Abdominal pain	0-10
Number of liquid stools	0-10
General well being	0-10
Examination	
Weight	0-10
Height	0-10
Abdomen	0-10
Perirectal disease	0-10
Extra-intestinal manifestations	0-10
Laboratory test: HCT , ESR	0-5
Albumin	0-10

Note. Adopted from "Development and validation of a pediatric Crohn's disease activity index" by Hyams et al., 1991, Journal of pediatric gastroenterology and nutrition, 12(4)449.

The Harvey-Bradshaw index (HBI). The Harvey-Bradshaw index was developed in 1980 to simplify the CDAI and does not require biochemical tests. The Harvey-Bradshaw Index is a simple tool use for long-term clinical trials (Vermeire, Schreiber, Sandborn, Dubois, & Rutgeerts, 2010). This index excludes some variables from CDAI (e.g., weight, hematocrit, and use of antidiarrheal). Table 2.5 provides the variables in HBI, and the total score equals the sum of the variables. The index utilizes 1-day measurements and consists of clinical parameters. The score ranges from 0 to 19; an HBI score of less than 5 is defined as remission, 5–7 indicates mild disease, 8–16 indicates moderately active disease, and more than 16 indicates severe disease. HBI is used for retrospective studies; however, CDAI requires prospective data (Best, 2006; Harvey & Bradshaw, 1980).

Table 2.5 The Harvey-Bradshaw index (HBI)

Variable	Score
General well-being	very well = 0 slightly below par = 1 poor =2 very poor = 3 terrible = 4
Abdominal pain	none = 0 mild = 1 moderate = 2 severe = 3
Number of liquid stools per day	N
Abdominal mass	none = 0 dubious = 1 definite = 2 definite and tender = 3
Complications	*1 point for each item* Arthralgia, uveitis, erythema nodosum, , aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess

Note. Reprinted from "A simple index of Crohn's disease activity" by Harvey J. and Bradshaw J., 1980, Lancet, 514.

Health-related quality of life (HRQOL). Health-related quality of life (HRQOL) is a subjective evaluation of the overall quality of life that affects physical or mental health. The inflammatory bowel disease questionnaire (IBDQ) is a validated tool and the most commonly used in IBD to assess health-related quality of life. It is a physician or self-administrated version and consists of 32 questions classified into four dimensions: bowel (10 questions), social (5 questions), systemic (5 questions), and emotional (12 questions). Scores for each question ranged from 1 to 7 points, with 1 (*poor*) to 7 (*best*). The total score ranges from 32 to 224 points, and the highest score indicates a better quality of life. This questionnaire significantly demonstrated the impact of quality of life on a patient's health (Desalvo, Bloser, Reynolds, He, & Muntner, 2005;

Dominick, Ahern, Gold, & Heller, 2002; Metelko et al., 1995; Selim et al., 2009). The questionnaire is provide in the appendix baseline form.

2.1.7 Dietary Factors in IBD

2.1.7.1 Nutritional assessment in IBD. Malnutrition is well documented in many chronic disease studies that include CD. Malnutrition has been reported in 70% to 80% of hospitalized active IBD patients (Hartman, 2009; Head et al., 2004; Leiper, Rushworth, & Rhodes, 2010). Most IBD patients suffer from nutritional deficiencies (75%) and weight loss (20 to 75%), which are the main symptoms of CD. Several factors may combine and contribute to cause undernutrition, such as a decrease in calorie intake (vomiting, anorexia), loss of calories (malabsorption, diarrhea), drug interactions, an imbalance of electrolyte and fluid and gut blood loss (Ferguson, Shelling, Browning, Huebner, & Petermann, 2007; Hartman, 2009; Head et al., 2004; Hébuterne, Filippi, Al-Jaouni, & Schneider, 2009; Leiper et al., 2010; Schneeweiss et al., 1999).

Nutritional deficiencies in vitamins, protein, and micronutrients have been found in most studies examining nutritional consequences in CD (Ferguson et al., 2007; Hébuterne et al., 2009). Low energy intake has been reported in about 40% of CD patients (Hartman, 2009; Sousa Guerreiro et al., 2007). Iron deficiency anemia due to blood loss was occurring in about 39.2% of CD patients (Vagianos, Bector, McConnell, & Bernstein, 2007). Vitamin D and C deficiency occurring from low serum levels of these nutrients were seen in 22% to 70% and 84% of CD patients, respectively (Filippi, Al-jaouni, Wiroth, & He, 2006; Vagianos et al., 2007). More than 50% of patients had vitamin C, zinc, and niacin deficiencies (Filippi et al., 2006).

A Canadian study conducted at the University of Manitoba in 2007 evaluated the nutritional assessment of IBD patients (Vagianos et al., 2007). Anthropometric measures, biochemical markers of nutrition, and food record assessment were recorded over 4 days. The

study found a high prevalence of inadequate vitamin E (63%), vitamin B_6 (29%), carotene (23.4%), vitamin B_{12} (18.4%), vitamin D (18%), albumin (17.6%), and 15.% of zinc (Vagianos et al., 2007). Vitamin D and iron supplements were recommended to avoid the complications from these nutritional deficiencies (Battat et al., 2014; Vagianos et al., 2007). Drug interactions are associated with nutritional deficiencies, steroids suppress calcium absorption in the intestine, and sulfasalazine reduces folate absorption (Alemzadeh et al., 2002).

2.1.7.2 Dietary intake and risk of CD. Research has demonstrated that a diet high in vitamins and minerals might play an important role in disease activity. Certain foods have shown to increase CD disease symptoms. A diet low in vegetables and fruits may increase the risk of Crohn's disease. An increased risk of developing CD was associated with increased consumption of sugar, sweeteners, sweets, fat, and red meat (Chapman-Kiddell, Davies, Gillen, & Radford-Smith, 2010; Hébuterne et al., 2009; Reif et al., 1997; Sakamoto et al., 1995). However, vegetables, fruits, fish, nuts, grains, and olive oil are inversely associated with CD (D'Souza et al., 2008).

Recent studies have used nutritional supplementation to control disease activity and nutritional deficiencies. Low serum concentrations in several nutrients indicate a need for micronutrient dietary supplements as a recommended daily intake for vitamins and minerals in addition to calories (Buchman, 2005; Head et al., 2004). Antioxidant treatment such as vitamin E (800 IU/d) and C supplements (1,000 IU/d) were found to decrease oxidative stress significantly in CD patients (Aghdassi, 2003). Moreover, high consumption of omega-3 fatty acids intake reduces CRP, IL-1, and TNF synthesis (Endres, 1996; Tsujikawa et al., 2000).

Regardless, patients still have a serious disease that affects their colons. Patients often need folate supplements to protect against colon cancer. Other patients may need calcium and vitamin D supplements to avoid bone problems (Arden & Cooper, 2002; Ba Lashner, Provencher,

Seidner, Knesebeck, & Brzezinski, 1997). The prevalence of vitamin D deficiency was significant in CD patients; however, the impact of vitamin D in regulating autoimmune system in CD is less understood.

2.1.8 Management of Crohn's Disease

2.1.8.1 Clinical medical management of Crohn's disease in adults. There is no cure for Crohn's disease, but a short-term goal is to provide medical treatment to control the symptoms by repressing inflammation and reaching remission. The long-term treatment goal is maintaining remission (CCFC, 2008). Medical therapy is determined by assessment of several points: severity, disease location, and the complications that the patient experiences. Each point is important to determine the type of medication to be used; some drugs work in a specific location in the bowel (e.g., aminosalicylate relives symptoms and inflammation in the left colon and rectum only). Other drugs such as budesonide affect ascending colon and ileum. In addition, severity is important because patients with severe disease may respond to a greater agent and vice versa (Bousvaros & Leichtner, 2012; Head et al., 2004).

Several groups of drugs are used to treat CD. Aminosalicylate (5-ASA) drugs are used to treat mild to moderate disease, and it can decrease the inflammation on the lining of the digestive tract (Bousvaros & Leichtner, 2012; CCFA, 2014b; CCFC, 2008). Corticosteroid drugs such as prednisone and methylprednisolone are used to treat moderate to severe CD disease by suppressing the entire immune system. Antibiotics can be used to treat infections such as abscesses and anal canal/vagina fistulas. In addition, immunmodulators medication such as azathioprine, methotrexate, and mercaptopurine can suppress or weaken the immune response. Biologic therapies such as TNF-agents consider the latest class of therapy used for CD patients who did not response well to the pervious medication. These drugs can lead to certain complications and side effects (Bousvaros & Leichtner, 2012; CCFA, 2014b; CCFC, 2008; Head

et al., 2004; Lichtenstein, Hanauer, & Sandborn, 2009). Mild to moderately active disease is typically treated with oral mesalamine or sulfasalazine. Moderate to severe diseases are treated with prednisone and infliximab (Lichtenstein et al., 2009).

Surgery is required for some CD patients when the medications fail or the patients have serious complications and are no longer responding to the medication (Jewell, 1998). Some patients may require resection surgery for a part of the intestine. Other patients consider removing all diseased sections if they experiences stricture, abscess, or obstruction (CCFC, 2008).

2.1.8.2 Current nutrition management of Crohn's disease. Nutrition therapy is an adjunctive part of the medical management of CD in adults. The goal of nutrition therapy is meeting patients' nutritional needs to restore nutritional deficiencies and to reduce symptoms (Beyer, 2008). Nutrition therapies consist of three applications. The first application is called exclusive enteral nutrition, which provides all nutritional needs through liquid formulas. This therapy promotes mucosal healing and suppresses inflammation in the intestine. The second application is called supplemental enteral nutrition, and it provides a supplement to a regular diet to increase nutrient and energy intake for maintaining remission. The third therapy focuses on micronutrient supplements to correct the deficiency e.g., vitamin D and calcium (Bousvaros & Leichtner, 2012).

Multivitamins supplementations are recommended along with folate (1–2 mg daily) and iron (10-15 mg) supplementations (Buchman, 2005; Eiden, 2003). The Recommended Dietary Allowance (RDA) recommend vitamin D 800 IU per day for CD patients with active disease especially in non-sunny cities (CCFA, 2014c). For CD patients suffering from severe malabsorption, a daily vitamin D supplement of up to 2,000–4,000 IU per day may be needed to correct the level of serum vitamin D (Eiden, 2003; Jeejeebhoy, 2002). The RDA for healthy

people for protein is 0.8 g/kg actual weight, whereas Crohn's patients who are free from renal disease require 1.0–1.5 g/kg body weight. Calcium supplements of 1,000–1,500 mg divided by thirds over the day are suggested (Eiden, 2003). Nutrition support has a significant impact in increasing patients' intakes to meet their daily nutrients requirements.

Dietary recommendations are important for CD patients; however, there is no specific recommendation to manage the disease activity in CD. Individuals must have a dietary recommendation prescribed to them depending on which part of the intestine is affected. Physicians instruct patients to avoid the foods that increase digestive problems. Low-fiber diets and adequate omega-3 fatty acids are suggested for active CD patients. Maintaining good health by having adequate intake of protein, nutrients, and calories is critical to managing CD symptoms (Beyer, 2008; Buchman, 2005; CCFA, 2014c; Eiden, 2003; Head et al., 2004).

2.2 Vitamin D

2.2.1 Vitamin D Background

Vitamin D is one of the first discovered fat-soluble vitamins (Holick, 2003; Institute of Medicine, 2010). Vitamin D (calcitriol) is considered a steroid hormone and is involved in regulating not only calcium and phosphorus concentrations and ensuring adequate bone mineralization, but also regulating immune system (Cranney et al., 2007; Institute of Medicine, 2010). The active form (1,25-dihydroxyvitamin D) synthesized not only in the kidneys but in other cells such as immune cells (Glerup et al., 2000; NHMRC, 2012).

2.2.2 Vitamin D Sources

Vitamin D exists as cholecalciferol (vitamin D_3), which is produced by skin cells or food of animal origin, and ergocalciferol (vitamin D_2), which is provided through plant (fungus) dietary sources (Brannon, Yetley, Bailey, & Picciano, 2008; NHMRC, 2012). The metabolite,

25(OH)D coverts calcitriol (1.25-dihydroxyvitamin D or 1,25$(OH)_2$D) which is the biologically active hormone that engages in physiological actions (NHMRC, 2012). The richest natural source of vitamin D is the sun. Dietary sources primarily include liver, egg yolks, veal, and fatty fish such as salmon, mackerel, tuna, and herring (Gropper, Smith, & Groff, 2009; Holick, 2004, 2008; Reichrath, 2008). Table 2.6 presents vitamin D content in some foods.

Food fortification with vitamin D helps people meet their daily nutritional requirements. In the United States, for example, juices, breakfast cereals, breads, milk, and cheese are fortified with vitamin D (Gropper et al., 2009; Holick, 2008). The extent of fortification in Canada is not as diverse as in the United States. Only milk and margarine have been considered for mandatory fortification in Canada in the amount of 400 IU per 250mL and 530 IU/100g, respectively. Other food items such as yoghurt, orange juice, and some meal replacement items are fortified in Canada; however, the amount of vitamin D is not considerable (Calvo, Whiting, & Barton, 2004; Calvo & Whiting, 2013; Health Canada, 2012).

Table 2.6 Vitamin D Content in Some Foods

Food	Serving size	Vitamin D µg/serving
Egg yolk, cooked	1	0.8
Tuna, Bluefin, cooked	75g	5.5
Canned tuna in water	75g	0.9
Beef liver, fried	75g	0.9
Salmon Sockeye, canned/bone	75g	13.9
Salmon Atlantic, baked/broiled	75g	5.1
Fortified milk	250 mL	2.5
Fortified margarine	10 g	2.5
Fortified orange juice	250 mL	1.3

Note. Derived from (Canadian Nutrient File, 2010).

2.2.3 Vitamin D Metabolism

Adequate exposure to solar ultraviolet radiation (295–300nm) can penetrate the skin when ultraviolet radiation is converted by 7-dehydrocholesterol to pre-vitamin D_3 (Holick, 1994; Reichrath, 2008). A biologically inert form of pre-vitamin D_3 stores in the epidermis and dermis undergoes isomerization reaction to convert pre-vitamin D_3 to cholecalciferol (M. Holick, 2004). After being synthesized in the skin, cholecalciferol and vitamin D acquired from the diet are joined to a vitamin D-binding protein (DBP) for transport to the liver. In the liver, $25(OH)D_3$ is the form that is enzymatically hydroxylated on carbon 25. Then, $25(OH)D_3$ is transported in blood. In the kidneys, vitamin D links to vitamin D receptor (VDR) and retinoid X receptor (RXR) heterodimers and transformed to become the active metabolite form 1, $25(OH)_2D_3$ when needed, which undergoes a second hydroxylation reaction on carbon 1. Vitamin D remain stored in adipose tissue for months and is released when needed (Brannon et al., 2008; Combs Jr, 2012; DeLuca, 2004; Holick, 1994, 1996, 2004; Jones, Strugnell, & Deluca, 1998; McCary & Deluca, 1999; Reichrath, 2008).

The active form of vitamin D has a separate pathway; it is play a role in involving immune system cells and links to VDR and RXR. The VDR and RXR then bind to the vitamin D response elements (VDRE) in the nucleus to function in the immune system (Veldhoen & Brucklacher-Waldert, 2012).

2.2.4 Physiological Actions of 1α, 25-dihydroxyvitamin D_3

2.2.4.1 Calcium and phosphate homeostasis and bone health. Vitamin D has a calciotropic function: controlling the homeostasis of calcium, phosphate, and bone mineralization. The essential role of vitamin D is to maintain and regulate calcium concentration in the plasma and to increase the level of serum Ca and phosphorus. When calcidiol is converted by the kidneys into the active form calcitriol (1,25-dihydroxycholecalciferol), the active form acts with PTH or alone

on three different target tissues: intestine, kidney, and bone (Combs Jr, 2012; DeLuca, 2004; Whiting & Calvo, 2005).

In the intestine, there is increased absorption of Ca^{2} and $Po_{4-;}$ however, in the kidney, there is increased reabsorption of Ca^{2+} only, which results in an increased level of Ca^{2+} in the plasma. Then, the $1,25(OH)_2D_3$ decreases the PTH level, which excretes and activates Po_{4-} reabsorption. Once in the bone, $1,25(OH)_2D_3$ stimulates PTH, which leads to an increased level of bone calcium (Brannon et al., 2008; Combs Jr, 2012; Deluca, 2004; Gropper et al., 2009; McCary & Deluca, 1999; Reichrath, 2008; Sauberlich & Machlin, 1992). Adequate level of calcium and vitamin D can protect children from developing osteomalacia and older adults from developing osteoporosis (Cranney et al., 2007; Institute of Medicine, 2010).

2.2.4.2 Vitamin D, the immune system, and diseases. Vitamin D has non-calciotropic functions in neuromuscular, cardiovascular, reproductive and immune systems, inflammation and cell growth. In addition, vitamin D helps genes encode proteins to regulate differentiation and cell proliferation (M. Holick, 2004, 2006; Institute of Medicine, 2010; NHMRC, 2012; Prentice, Goldberg, & Schoenmakers, 2008; Whiting & Calvo, 2005). The epidemiological evidence indicates that there is a relationship between low levels of vitamin D and many other diseases, including cancer, diabetes, autoimmune disease, cardiovascular disease, schizophrenia, and depression (Holick, 2007; Prentice et al., 2008; Reichrath, 2008). Moreover, an insufficient level of vitamin D has an impact on fetal and pubertal growth and places the elderly at greater risk for acquiring chronic degenerative diseases (Prentice et al., 2008).

***Vitamin D and immunologic function*.** As mentioned in the section on vitamin D metabolism, the immune system cells can make the active $1,25(OH)_2D_3$ form, which binds to VDR-RXR. Once VDR-RXR link to $1,25(OH)_2D_3$, they bind to response elements (VDRE) in the nucleus to function in the immune system (Veldhoen & Brucklacher-Waldert, 2012). The active

form then functions on several types of immune cells. In dendritic cells (DCs), $1,25(OH)_2D_3$ acts to decrease production of maturation in IL-12, IL-6, and IL-23. The effect of B cells and antibody-secreting cells is decreasing proliferation as well as IgG, IgM, and plasma cell differentiation. Moreover, inhabitation of T cell stimulation results in response by $T_h1$and T_h17 cells and enhances T_h2 and T_{reg} activity (Aranow, 2011; Veldhoen & Brucklacher-Waldert, 2012). Table 2.6 Important Markers of Inflammation and their Functions.

Vitamin D receptor polymorphisms and diseases. The vitamin D receptor (VDR) gene, a member of the NR1|1 nuclear receptor family, has biological functions on vitamin D_3 (Moore et al., 2006; Szpirer et al., 1991). VDR hormones, heterodimer, and retinoid-x receptors bind with specific vitamin D-response elements (VDRE) on DNA and initiate the transcriptional pre-initiation complex with other nuclear proteins. This VDR gene causes important effects on metabolism, affecting calcium, immune function, and gene activation (Valdivielso & Fernandez, 2006). A polymorphism of the vitamin D receptor (VDR) gene changes in at least 1% of the population. The changes exist in non-coding parts, and they effect the expression degree of the gene and the protein levels (Valdivielso & Fernandez, 2006). The polymorphism (genetic variants) is associated with susceptibility of some diseases (Simmons, Mullighan, Welsh, Jewell, & Unit, 2000).

Recent evidence has linked VDR polymorphisms with cancer, nephrolithiasis, diabetes, UC, CD, and other diseases. In CD, there is a relationship between CD susceptibility and VDR gene; this gene influences BMD as well (Simmons et al., 2000; Todhunter et al., 2005). However, conflicting results have been reported regarding the association between VDR and cancer, bone biology, blood pressure, diabetes, and autoimmune disorders such as hepatitis, CD, Graves' disease, and multiple sclerosis. In CD, the relationship between Tag1, Apa1, and Fokl polymorphisms and the disease has been reported. Indeed, several factors such as diet and

latitude influence the VDR (Simmons et al., 2000; Valdivielso & Fernandez, 2006).

***Vitamin D, chronic and autoimmune diseases*.** A number of studies have demonstrated that patients with autoimmune disease have a low level of vitamin D. The dose of vitamin D supplementation that is required to decrease PTH in autoimmune diseases is different in each condition (Romagnoli, Pepe, Piemonte, Cipriani, & Minisola, 2013). In a chronic disease, researchers suggested that people with higher BMI have lower vitamin D levels, but fat content itself is a stronger factor than BMI in inverse relationship with serum 25(OH)D concentration (Vimaleswaran et al., 2013). The Endocrine Society guidelines recommend that obese people take vitamin D supplements two or three times higher than healthy people do (M. Holick et al., 2011). Other studies found that 4,000 to 10,000 IU/d of vitamin D supplementation had a significant effect on glycemic indices (Belenchia, Tosh, Hillman, & Peterson, 2013; Nagpal, Pande, & Bhartia, 2009).

Moreover, a low level of serum vitamin D was found in patients with multiple sclerosis due to low dietary vitamin D intake and indoor activities in fall and winter (Cantorna, 2006; Weinstock-Guttman et al., 2012). A low risk of rheumatoid arthritis in older women aged above 55 years old was associated with high doses of vitamin D intake (Merlino et al., 2004). A daily intake of vitamin D supplementation (2,000 IU) had protective impact on risk of developing diseases related to vitamin D deficiency in children. Research found that 400 IU/d of vitamin D intake may decrease the risk of rheumatoid arthritis and multiple sclerosis by 40% (M. Holick, 2005; Whiting & Calvo, 2005).

Table 2.7 Important Markers of Inflammation and their Functions.

Markers of inflammation	Immune cells	Nature	Function
T_h1	T cells	Adaptive immune response	Develop intracellular bacterial or virus infection
T_h2	T cells	Adaptive immune response	• Antibody-mediated against parasites, asthma, allergy, bacteria • Eosinophil activation • Several macrophage functions inhabitation
T_h17	T cells	Adaptive immune response	Inflammation (bacteria, fungi) and injury in the skin and GI tract
T_{reg}	T cells	Adaptive immune response	• Regulation immune response • Maintaining immune tolerance • Preventing autoimmune diseases
IL-6	mononuclear, phagocytes dendritic cells T cells	Anti-inflammatory cytokine	Induction the acute phase protein response
IL-12	Monocytes, macrophages dendritic cells B cells	Pro-inflammatory cytokine	Enhancing interferon-$_\gamma$, IL-2 and TNF-α from T cells and NK cells
IL-23	macrophages dendritic cells	Anti-inflammatory cytokine	regulation T_h17 proliferation and function

Note. Adapted from (Iwakura & Ishigame, 2006; Romagnani, 1999; R. J. Simpson, Hammacher, Smith, Matthews, & Ward, 1997; Stockinger & Veldhoen, 2007; Vignali, Collison, & Workman, 2008; Wolf, Sieburth, & Sypek, 1994).

2.2.5 Assessment of Vitamin D Status

According to the U.S. Institute of Medicine (2010), a plasma concentration of 25-hydroxyvitamin D is considered the best biomarker to measure vitamin D status; this represents the sum of vitamin D in dietary intake (diet and supplements) and cutaneous synthesis. Conversely, the biological active form of calcitriol $1,25(OH)_2D$ is not considered a reliable marker to assess vitamin D status because it is under homeostatic control and has a short half-life (Hollis, 2005, 2007). Plasma PTH concentration has been reported as a functional index of vitamin D status because of the inverse relation between 25(OH)D and PTH. When insufficient levels of vitamin D exist, PTH secretion is elevated because of poor calcium absorption or low dietary calcium intake. The level of PTH concentration depends on many factors, including demographics, dietary Ca, kidney function, and drug use, so the PTH level varies widely among individuals, and making it difficult to define the normal level of PTH (Institute of Medicine, 2010; Prentice et al., 2008).

The most recent update of vitamin D dietary intake assessment from the Institute of Medicine was in 2011. Subclinical deficiency is associated with concentrations of 30–50 nmol/L (12–20 ng/mL), and vitamin D deficiency is considered when the concentration is below 30 nmol/L (< 12 ng/mL). Some findings suggested that a concentration of 25(OH)D ≤ 80 nmol/L (32 ng/mL) is an insufficient vitamin D level; a plateau in parathyroid hormone (PTH) concentration is observed at 80 nmol/L (M. F. Holick, 2005; Mullin & Dobs, 2007). An optimal concentration of serum 25-dihydroxyvitamin D_3 is indicated as above 50 nmol/L.

Hypervitaminosis D can occurs when taking a daily vitamin D supplementation above 10,000 IU. Adverse effects are associated with serum concentrations >125 nmol/L (>50 ng/mL; Institute of Medicine, 2010). Vitamin D is considered potentially toxic when serum $25(OH)D_3$ levels exceed 500 nmol/L (200 µg/L; Institute of Medicine, 2010; Vieth, 2006 ; Jones, 2008). The

main consequence of vitamin D toxicity is hypercalcemia, which can cause over calcification on kidney, bones, heart and soft tissues (Dionne, Abitbol, & Flynn, 2012). In addition, constipation, loss of appetite, fatigue, vomiting, muscle weakness and dehydration are symptoms of hypervitaminosis D (Cusano, Thys-Jacobs, & Bilezikian, 2011; Vieth, 1999, 2007). Table 2.8 presents serum 25 (OH)D concentrations and health.

Table 2.8 Serum 25-Hydroxyvitamin D [25(OH) D] Concentrations and Health

Vitamin D status	**Range** **Units (nmol/L) or (ng/mL)**	
Vitamin D deficient	<30 nmol/L	<12 ng/mL
Subclinical deficiency	30–50 nmol/L	12–20 ng/mL
Optimal level	>50 nmol/L	20 ng/mL
Toxicity	>125 nmol/L	>50 ng/mL

Note. Adapted from "Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards" by Vieth , 2006, The journal of nutrition, *136*(4), 1117-1122 and "Food and Nutrition Board, Dietary Reference Intakes for Calcium and Vitamin D" by Institute of Medicine, 2010, National Academy Press.

2.2.6 Recommendations of Vitamin D Intake

The Food and Nutrition Board (FNB) at the Institute of Medicine has set dietary reference intake (DRI) values for daily vitamin D intake for different age groups to ensure adequate calcium metabolism and healthy bones. The Institute of Medicine (2010) stated that the intake of vitamin D above the standard of recommended dietary allowance (RDA) has no extra health benefits. The RDAs for vitamin D with minimal sunlight exposure are expressed in international units (IUs) and micrograms (mcgs) while 40 IU is equal to 1 mcg. The RDA, estimate average requirements (EAR), and tolerable upper intake level (UL) of vitamin D are provided in Table

2.9. Toxicity is considered more than 10,000 IU/day (Institute of Medicine, 2010). A review conducted in 2014 examined changes in serum vitamin D with oral vitamin D supplementations in healthy people. The researchers summarized studies with the amount of vitamin D supplements and changes in the serum (Jarrett, Ducasa, Buller, & Berwick, 2014). The lowest change was found in people who were treated with 200 IU/d vitamin D_3 for a year—baseline 37.4 and after 46.4 nmol/L (change in serum level 8.9 nmol/Lo; Al-Shaar, Mneimneh, Nabulsi, Maalouf, & Fuleihan, 2014). The highest change was noted with people who were taking 10,000 IU/d for 20 weeks—baseline 65.6 and after 225 nmol/L (change in serum level 159.4 nmol/L; Heaney, Davies, Chen, Holick, & Janet Barger-Lux, 2003).

Table 2.9 Dietary Reference Intakes (DRIs) Values for Vitamin D

Age group	**Recommended Dietary Allowance (RDA) per day**	**Estimated Average Requirement (EAR) per day**	**Tolerable Upper Intake Level (UL) per day**
Infants 0-6 months	400 IU (10 mcg) *	-	1000 IU (25 mcg)
Infants 7-12 months	400 IU (10 mcg) *	-	1500 IU (38 mcg)
Children 1-3 years	600 IU (15 mcg)	400 IU (10 mcg)	2500 IU (63 mcg)
Children 4-8 years	600 IU (15 mcg)	400 IU (10 mcg)	3000 IU (75 mcg)
Children and Adults 9-70 years	600 IU (15 mcg)	400 IU (10 mcg)	4000 IU (100 mcg)
Adults > 70 years	800 IU (20 mcg)	400 IU (10 mcg)	4000 IU (100 mcg)
Pregnancy/ Lactation	600 IU (15 mcg)	400 IU (10 mcg)	4000 IU (100 mcg)
*Adequate Intake rather than Recommended Dietary Allowance			

Note. Reprinted from "Food and Nutrition Board, Dietary Reference Intakes for Calcium and Vitamin D" by Institute of Medicine, 2010, National Academy Press.

2.2.7 Vitamin D Deficiency

2.2.7.1 Epidemiology of vitamin D deficiency in Saudi Arabia. Vitamin D deficiency is widespread in children and adults (Tangpricha, Pearce, Chen, & Holick, 2002). There are one billion people suffering from vitamin D deficiency or hypovitaminosis in the world (M. Holick, 2006; Lips et al., 2006). The Middle East, in particular Saudi Arabia, has registered one of the highest rates of rickets and hypovitaminosis D worldwide (Baroncelli et al., 2008; El-Hajj Fuleihan, 2009; Kimball, Fuleihan, & Vieth, 2008; Lips et al., 2006). Saudi Arabia has a great deal of sunlight, but fortified products with vitamin D such as fluid milk, powdered milk, and yogurt are limited to specific brands. The amount of vitamin D in fluid milk and yogurt is 40–400 IU/L, and in powdered milk, it is 65.6 IU/100g–350 IU/100g (Sadat-Ali, Al Elq, Al-Farhan, & Sadat, 2013).

It was found that 80% of adolescent Saudi girls had low serum 25(OH)D levels (below 25 nmol/L), and a 25(OH)D level of 10 to 30 nmol/L was found in elderly females and female university students (Sedrani, Elidrissy, & El Arabi, 1983; Siddiqui & Kamfar, 2007). The deficiency was found in 59% of newborn samples at King Khaled University Hospital in Riyadh, Saudi Arabia; 87.5% of newborns had levels of vitamin D below 50 nmol/L, which is considered insufficient (25–50) and deficient (< 25; Alfaleh et al., 2014). Elsammak et al. (2011) conducted a study on healthy young Saudis mean age 30 for male and 31 female (M = 30, F = 31) in the eastern region of Saudi Arabia. The researchers found low levels of serum 25(OH)D in both males (10.1ng/mL) and females (9.9ng/mL). The prevalence of vitamin D deficiency is extremely high despite that more than 90% of the participants had adequate dairy products and that more than 65% had enough exposure to sunshine (Elsammak, Al-Wossaibi, Al-Howeish, & Alsaeed, 2011).

Some possible explanations for these low vitamin D levels include an indoor lifestyle, avoiding the strong heat of the sun (latitude 15–26°N), lack of awareness, and cosmetic preferences (i.e., frightened of getting a darker skin tone from the sun's rays; Christie & Mason, 2011; Elsammak, Al-Wosaibi, Al-Howeish, & Alsaeed, 2010; Elsammak et al., 2011; Mithal et al., 2009; Siddiqui & Kamfar, 2007). Increasing calcium homeostasis, age, and weight were significantly associated with vitamin D deficiency (Alfawaz, Tamim, Alharbi, Aljaser, & Tamimi, 2014). Testing for vitamin D among children and women is highly recommended. A powerful health policy for vitamin D supplementation and the application of dietary health are required to meet people's needs of vitamin D (Hussain, Alkhenizan, El Shaker, Raef, & Gabr, 2014).

2.2.7.2 Epidemiology of vitamin D deficiency in Canada: Vitamin D levels are low in many healthy people, especially in winter. Canadian researchers examined healthy men and women at the end of the winter season in Calgary, Alberta, which is located in the western part of the country and has more hours of sunshine than do other Canadian cities. The researchers found that 20% of the samples had low serum concentration (< 40 nmol/L), 39% were below 50 nmol/L, and most participants (86%) had levels of serum < 80 nmol/L. Serum concentrations were found to be even lower in summer, with levels of 9%, 14%, and 68%, respectively. This might be related to many people travelling during the summer to countries that are below latitude 42° N (Rucker, Allan, Fick, & Hanley, 2002). Likewise, vitamin D levels can differ based on ethnicity. Vieth et al. (2001) studied the prevalence of hypovitaminosis in young women (ages 18–35) in Toronto and found 21% of Caucasian women, 32% of non-White women and 25% of women from Africa had low levels of serum 25(OH)D (< 40 nmol/L; Vieth, Cole, Hawker, Trang, & Rubin, 2001).

Dr. Whiting and coworkers (2011) evaluated vitamin D status in Canadians ages 6–79 years to determine whether Canadians met specific DRI recommendations. The researchers reported that 25% of these Canadians did not meet their RDA; more than 33% of Canadians did not take supplements in the winter and thus did not meet their RDA levels. The highest risk groups were found in non-Caucasian Canadians (Whiting, Langlois, Vatanparast, & Greene-finestone, 2011). Other researchers conducted a study using data from CHMS 2007 to 2009 to indicate the prevalence of vitamin D deficiency among Canadian populations. Vitamin D deficiency was found in 4% of Canadians, whereas 90% had adequate concentrations (≥ 37.5 nmol/L) for bone health (Langlois et al., 2010).

Dr. Vatanparast and others conducted a study in 2010 to evaluate vitamin D intake using data from food intakes of Canadians reported in a 2004 Canadian Community Health Survey Cycle 2.2 (CCHS 2.2); the sample size was 34,789 persons ages over 1 year. The results demonstrated that women in all age groups had lower vitamin D intake than did men; White Canadians had a higher intake than Canadian minorities, which were 49% and 31.1%, respectively. Foods with the highest sources of vitamin D that were consumed included milk, meat, and meat alternatives. Canadian populations consume vitamin D from food less than the vitamin D dietary recommendation (Vatanparast, Calvo, Green, & Whiting, 2010). Table 2.10 Summarize the Main Results from Different Studies on 25(OH)D Status.

Table 2.10 Summarize the Main Results from Different Studies on 25(OH)D Status

City	(n)	Season	Vitamin D status (nmol/L)	Reference
Whole Canada	5306	all season	67.7	(Langlois et al., 2010)
Toronto	155	fall	44.9	(Liu et al., 1997)
Edmonton	36	summer	122	(Overton & Basu, 1999)
Calgary	188	winter	57.3	(Rucker et al., 2002)
Quebec	741	winter	64.9	(Sinotte, Diorio, Bérubé, Pollak, & Brisson, 2009)

2.2.8 Consequences of low vitamin D status. Low levels of vitamin D are the result of an inadequate dietary intake, limited sun exposure, and other factors. Consequences include a lack of intestinal absorption of dietary calcium and phosphors (loss into urine), hyperparathyroidism (a low serum phosphor level), reduced bone mineralization, and increased cortical bone loss, which might be associated with osteoporosis and hip fractures (Bouillon, R., De Groot, L. J., & Jameson, 2001; M. Holick, 2004; Institute of Medicine, 2010; Lips, 2001; Rizzoli & Bonjour, 2004). Moreover, the risk leads to a softening of the bones known as rickets in children and osteomalacia in adults. These diseases are due to impaired bone mineralization and might cause muscle weakness, bone pain, and skeletal deformities (Bakhtiyarova, Lesnyak, Kyznesova, Blankenstein, & Lips, 2006; Bender, 2003; Holick & Chen, 2008; M. Holick, 2007; R. U. Simpson, Thomas, & Arnold, 1985).

Vitamin D receptors exist in human skeletal muscle tissue and its deficiency has been associated with increased body sway and high incidence of fractures (Bischoff-Ferrari et al., 2004; Holick & Chen, 2008; R. U. Simpson et al., 1985; Visser, Deeg, & Lips, 2003). A skeletal

mineralization defect might occur in adults as well. The non-mineralized osteoid leads to weak structural support and flexibility to the covers of the periosteal surface, which causes joint and muscle aches and pains (Al-Ali & Fuleihan, 2000; Malabanan, Turner, & Holick, 1998).

Low levels of vitamin D result in many other serious health problems. New evidence has shown that a vitamin D deficiency is associated with an increased risk of developing cancers e.g. breast and prostate cancer, multiple sclerosis (MS), diabetes, and cardiovascular disease (Davis, 2008; Hassan et al., 2013; Higgins et al., 2013; Holick, 2005; Munger, Levin, Hollis, Howard, & Ascherio, 2006; Pittas et al., 2006). Epidemiological studies reported that individuals who have low levels of vitamin D are at greater risk of developing colon cancer (Bostick et al., 1993; Garland et al., 1985; Kearney et al., 1996; Martinez et al., 1996). Women who live in areas with lower levels of sunlight had low serum $1,25(OH)_2D$ and were at five times greater risk of developing breast cancer (Garland, Gorham, & Young, 1990; Gorham, Garland, & Garland, 1989; Vieth et al., 2007). Dietary vitamin D intake was associated inversely with development of MS (Munger et al., 2006). In type 2 diabetes, endothelial function was improved by taking a single dose of 100,000 IU vitamin D_2 supplementation (Sugden, Davies, Witham, Morris, & Struthers, 2008).

2.2.9 Factors that influence vitamin D status. A number of factors influence vitamin D levels and absorption. These factors include environmental factors such as latitude (distance from the equator), atmospheric particulate matter, cloud cover, seasons, time of day, and individual factors including skin tone (i.e., dark skin), age, use of sunscreens, and clothing (i.e., veils, long sleeves or pants; Batieha et al., 2011; Holick, 2008; NHMRC, 2012; Tsiaras & Weinstock, 2011).

***Environmental factors that influence vitamin D status*.** Seasonal changes significantly affect cholecalciferol production. Vitamin D deficiency is more common during the winter period because the UVB radiation is not strong enough to produce adequate vitamin D (Burgaz,

Akesson, Oster, Michaëlsson, & Wolk, 2007; Holick, 1996; NHMRC, 2012). Moreover, the solar zenith angle (SZA) has a significant impact on UV production. When the sun is most directly overhead, the smallest SZAs cause stronger UV radiation. To illustrate, in the winter and fall when the sun is closer to the horizon, SZA increases, and the amount of UV radiation that spreads across the planet is reduced significantly (Holick, 1995; Kimlin, 2008; Webb & Engelsen, 2008).

According to Burgaz et al. (2007), studies have demonstrated that complete cloud cover may decrease UV radiation by 50%, shade reduces UV by 60%, and the angle of the sun, distance from the equator, and latitude influence vitamin D production in human skin. Vitamin D_3 in countries at higher latitudes is not produced during the winter, whereas countries at lower latitudes (i.e., below 35°N) have vitamin D_3 production that is sufficient for the entire year (e.g., the latitude of Canada is 45° N, 75° W), and the latitude of Saudi Arabia is 24° N and 45° E; Rehman, Halawani, & Mohandes, 2003; Tsiaras & Weinstock, 2011; Ward, Gaboury, Ladhani, & Zlotkin, 2007). In other words, the change of seasons or weather conditions and geographic latitude can lead to larger or smaller rates of SZA that affect UV production. Consequently, this change causes changes in the production of vitamin D in humans.

Individuals and lifestyle factors influence vitamin D status. Aging significantly reduces the synthesis of vitamin D in the skin. People younger than age 50 have the ability to create and store vitamin D for approximately six months, and it remains usable when there is a low production of vitamin D during the winter. Skin thickness, however, decreases linearly in humans after age 20. The effectiveness of producing 7-dehydrocholesterol by skin cells decreases substantially from 100% to 25% in adults (Holick, 1995, 1996, 2008). Darker skin has a greater amount of melanin, which is an efficient protector against absorption of UV radiation, but melanin decreases the skin's ability to produce vitamin D. Darker skin tones are more likely to

have a vitamin D deficiency and require approximately five to ten times longer sunlight exposure than do other ethnicities (with lighter skin tones) for the same level of absorption (Holick & Chen, 2008; Holick, 2008; Institute of Medicine, 2010). Obese people have serum vitamin D 15 nmol/L lower than do non-obese people with no difference between women and men (Snijder et al., 2005).

Using sunscreen and covering the skin with layers of clothing are also factors that can contribute to vitamin D deficiency. Skin synthesizes only a small amount of vitamin D when sunscreen with an SPF of eight or higher is applied, and sunscreen dramatically reduces UV absorption (Holick, 1994, 1995). According to Holick (1994), wearing layers of clothing in a cold climate is a factor that prevents cutaneous cholecalciferol production. In some societies, people cover most sun-exposed areas for religious and cultural reasons, and these people are at a greater risk than others are of vitamin D deficiency (Batieha et al., 2011; Holick, 1994). A study conducted by Guzel et al. (2001) aimed to compare vitamin D status in Turkish veiled and unveiled women. The study demonstrated that veiled Turkish women could not synthesize sufficient vitamin D in their bodies. The researchers concluded that Turkish women who cover their whole body had vitamin D deficiency, and dietary vitamin D supplements were recommended (Guzel, Kozanoglu, Guler-Uysal, Soyupak, & Sarpel, 2001).

Similarly, Mishal (2001) conducted a study in Jordan to evaluate vitamin D status, and the effect of different styles of clothing on vitamin D metabolism in healthy young Jordanian women. Many women in Jordan cover the entire body for religious reasons (the same is true in Saudi Arabia); some cover their hands and faces, whereas others wear Western styles (i.e., do not cover up as much). The sunlight exposure in Jordan is adequate in summer but not in the winter. There is also a lack of vitamin D fortification products and fish consumption. Vitamin D deficiency was found in 83.3% of woman who wore full-coverage clothing during summer and in

81.8% in winter. In women who were not fully covered, 54% were vitamin D deficient in summer and 77.6% in winter, and finally, for Western dress styles, 30.8% of women were vitamin D deficient in summer and 75% in Jordan winter. As a result, covered women are more likely to have a vitamin D deficiency than are women who wear Western dress styles; however, there was no statistical significance observed between different dress styles (Mishal, 2001).

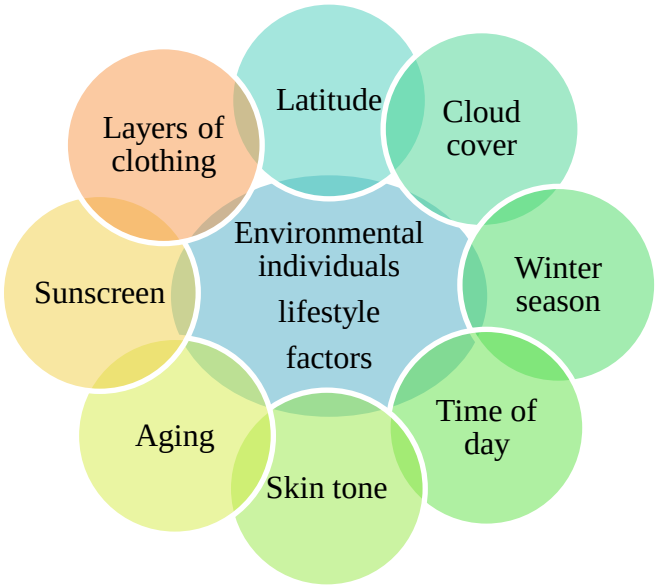


Figure 2.1 Environmental, individuals and lifestyle factors influencing vitamin D levels.

2.3 Vitamin D and Crohn's Disease

2.3.1 Prevalence of Vitamin D Deficiency in IBD

There is a link between vitamin D and IBD. Vitamin D deficiency is common in IBD patients, especially those with Crohn's disease, where 18–70% of patients are vitamin D deficient, and 45% have metabolic bone disease (de Bruyn et al., 2014; Siffledeen et al., 2005; Suibhne, Cox, Healy, O'Morain, & O'Sullivan, 2012a; Vogelsang et al., 1989). In 2008, Leslie et al. conducted a Canadian study in Manitoba that found that 88% of IBD patients (56 CD and 45 UC) had plasma vitamin D below 75 nmol/L. In Wisconsin in the United States, another study examined 403 CD and 101 UC patients and found that 11% of IBD patients had vitamin D levels

below 10 ng/dL, and 50% were below 30 ng/dL (Ulitsky et al., 2011). Of the 81 CD patients, 63% were deficient (<50 nmol/L; Suibhne, Cox, Healy, O'Morain, & O'Sullivan, 2012).

Later, Alkhouri, Hashmi, Baker, Gelfond, and Baker (2013) examined 61 IBD patients and found that 62% of IBD patients, compared with 75% of the control group, had low vitamin D levels. Another study that was conducted in summer found that 95% of 65 IBD Iranian patients were deficient, with vitamin D levels below 30 ng/mL (Hassan et al., 2013). In addition, recent study shows vitamin D deficiency was low in CD cases and a healthy control group with no significant difference with mean 25(OH)D 51.6nmol/L in CD, and 60.8 nmol/L in controls. The study found non-Caucasian, high level of BMI, sun protection, and no holidays in the last year were associated significantly with serum vitamin D levels in CD cases (de Bruyn et al., 2014). However, another study found that 19% of 70 CD, five UC, and three IBDU were vitamin D deficient (< 51 nmol/L; Levin et al., 2011). Similarly, in Boston, Massachusetts, researchers examined 1,763 CD and 1,454 UC and reported that 28% of IBD were insufficient (20–30 ng/mL) and that 32% were deficient (< 20 ng/mL; Ananthakrishnan et al., 2013).

2.3.2 Serum Vitamin D and Crohn's Disease

Serum 25(OH)D concentrations correlate well with disease activity, nutritional status, bone mineral density (BMD), and quality of life (Abreu et al., 2004; Harries et al., 1985; Ulitsky et al., 2011). Researchers found vitamin D deficiency is associated with high disease activity and CDAI scores, severe Crohn's disease (known as a low level of albumin), and low HRQOL scores along with patients who do not take vitamin D supplements and those in an early diagnosis stage. Decreasing vitamin D levels is associated with high levels of CRP and ferritin, low nutritional status, smoking, insufficient sun exposure, and small bowel involvement (Pappa et al., 2006; Suibhne et al., 2012a; Ulitsky et al., 2011). Patients who have active CD disease and have little to no sunlight exposure were found to have low serum 25(OH)D levels (Joseph et al., 2009). Ham et

al. (2014) concluded that the level of vitamin D increases after treating infliximab in active CD patients. In both UC and CD patients, an increased risk of surgery and hospitalization are associated with low plasma $25(OH)_2$ D, and an optimal level of $25(OH)_2$ reduced the risk of surgery in CD patients (Ananthakrishnan et al., 2013). New study found no significant association between seasonal vitamin D levels and disease activity (Kini, Young, Herbison, & Schultz, 2014). Koutkia, Lu, Chen, and Holick (2001) conducted a case report examining treatment of vitamin D deficiency with tanning bed UVB radiation in CD patients. After 4 weeks of treatment, PTH decreased by 52%, calcium increased from 7.8 to 8.5mg/dL, and serum vitamin D increased significantly from 7 to 32 ng/mL.

Bone health is one of the main concerns in CD cases. A study reported a significant negative correlation exists between vitamin D levels and BMD in CD patients who use glucocorticoid. Two independent risk factors were associated with low BMD and osteoporosis, high levels of $1,25(OH)_2D$, and use of glucocorticoid (Abreu et al., 2004). Low BMD is common in CD patients with ileostomy and low body mass index (Gupta, Wu, Moore, & Shen, 2014). However, another study found that patients who have vitamin D deficiency are not at a higher risk of low BMD (Pappa et al., 2006). Low levels of 25(OH)D can cause a reduction in calcium absorption that enhances the parathyroid hormone (PTH), which regulates serum calcium and phosphate (Abreu et al., 2004; Joseph et al., 2009). Vitamin D and K potentially maintain bone health in IBD, whereas several factors may influence bone health (e.g., inflammatory cytokines, reduced exposure to sunlight, and steroid use; Iijima, Shinzaki, & Takehara, 2012).

According to current evidence, the main role of vitamin D in CD patients is to promote bone health and to decrease the risk of inflammation and cancer. There is an increased risk of cancer, especially colorectal cancer, in CD patients with low vitamin D levels; each 8% reduction risk of colorectal cancer was associated with an increase in the level of serum vitamin D by 1-

ng/mL (Abreu et al., 2004; Ananthakrishnan et al., 2014; Edward D. Gorham et al., 2007; Holick, 2004; Jørgensen et al., 2010; Van Assche et al., 2010). Moreover, CD patients with a BMI greater than or equal to 25 are more likely to have a low level of vitamin D (< 20 ng/mL; Singla et al., 2014). Appendix 1 table 2.11 presents studies on vitamin D and IBDs including one systematic review, three clinical trials, five cohort studies, four case- control studies, three cross-sectional studies, and one review of four patients' medical records. Nine of the studies had focused on IBDs and seven studies on CD. The minimum dose of vitamin D was 400/d IU and the maximum 10,000 IU/d.

2.3.3 Guidelines of Vitamin D Supplementation in Crohn's Disease

The Institute of Medicine RDA guidelines for healthy people ages 9 to > 70 years, including pregnant and lactating women, is 600 IU/day and upper level 4,000 IU/day. Holick et al. (2011) recommend a daily vitamin D supplement up to 1,500–2,000 IU in order to achieve 25(OH)D in plasma ≥ 30 ng/mL in people with low vitamin D levels. The doses should be increased by a factor of two to threefold in obese or people who are taking anticonvulsant drugs. In addition, CD patients require higher daily vitamin D intake than healthy people do. In case of malabsorption syndrome, small bowel involvement, and a BMI > 30, the dosage should be multiplied by a factor of 1.5–3. Physicians recommend that CD patients with a vitamin D deficiency take oral cholecalciferol up to 50,000 IU once a week for 8 weeks or until patients achieve serum 25(OH)D 30–36 ng/mL (Basson, 2013; Garg, Lubel, Sparrow, Holt, & Gibson, 2012; Holick et al., 2011; Zhou, LeBoff, & Glowacki, 2010). In cases of severe vitamin D deficiency, a cholecalciferol supplement up to 300,000 to 600,000 IU is considered safe and effective, but monitoring Ca levels is required (Basson, 2013; Binkley et al., 2011; Trang et al., 1998). Table 2.12 presents vitamin D supplementation guidelines for CD patients.

Table 2.12 Vitamin D Supplementation Guidelines for CD Patients.

Serum vitamin D		Oral vitamin D_3 supplementation
(ng/mL)	**(nmol/L)**	
≤3	≤8.5	5000 IU/day
4≤ 9	8.6≤23.5	4000 IU/day
10 ≤15	23.6≤38.4	3000 IU/day
16≤ 23	38.5≤58.4	2000 IU/day
24 ≤ 29	58.5≤73.4	1000 IU/day
30 - 36	73.5-89.9	1500- 2000 IU/day*

* Maintenance doses should be performed for 3 months, and then 3-6 months adjusting the doses until the target is achieved.

Note. Adapted from "Vitamin D and Crohn's Disease in the Adult Patient: A Review." by Basson, 2013, Journal of parenteral and enteral nutrition, *38*(4), 438-458.

2.3.4 Vitamin D Supplementation in Crohn's Disease

High 25(OH)D levels from a high dose of vitamin D supplementation may have health benefits that can prevent a relapse of Crohn's disease (Jørgensen et al., 2010; Miheller et al., 2009). Several studies sought to achieve an optimal level by comparing different doses of vitamin D. In 2014, researchers assessed vitamin D levels in children with CD and examined whether vitamin D_3 supplementation with 400 to 2,000 IU/d for 6 months reduced the deficiency below the cut-off of 20–30 ng/mL. The researchers found that 2,000 IU/d vitamin D_3 supplementation was elevating plasma 25(OH)D above 30 ng/mL more effectively than 400 IU/d (Wingate et al., 2014). A recent study sought to maintain optimal vitamin D levels in children with IBD by having the children receive 400 IU/d of vitamin D_2 versus 2,000 IU/d in winter and spring and

1,000 IU/d in summer and fall. It has been noted that a daily vitamin D_2 supplementation up to 2,000 IU was insufficient to maintain the optimal levels in children with IBD (Pappa et al., 2014).

Researchers conducted a study involving pediatric patients with IBD (5–21 years of age) that had them receive either a daily 2,000 IU of vitamin D_2, 2,000 IU of vitamin D_3, or 50,000 IU of vitamin D_2 weekly for 6 weeks. The researchers found that 2,000 IU of vitamin D_3 and 50,000 IU of vitamin D_2 were raising plasma 25(OH)D and were well tolerated by the patients (Pappa et al., 2012). A randomized, placebo-controlled trial conducted by Jorgensen (2010) examined the benefits of $1,25(OH)_2\ D_3$ therapy. CD patients (n = 108) in remission received both vitamin D_3 (1,200 IU) and calcium (1,200mg/d) or calcium (1,200mg/d; placebo) for a year. After 3 months of treatment, oral vitamin D_3 increased the levels of 25(OH)D from a mean of 69 to 96 nmol/l. Furthermore, the study considered 1,200 IU/D of vitamin D_3 as a high dose, but now high doses of 2,000 IU/D or more are considered safe without the risk of hypercalcemia (Jørgensen et al., 2010).

Studies also examined the effect of different doses of vitamin D on disease activity. Researchers investigated the effect of 1, 25-dihydroxyvitamin D and 25(OH)D on disease activity and bone metabolism. The results indicated that CDAI and CRP decreased dramatically after 6 weeks, but this effect disappeared at the end of the trial (at 12 months). In addition, active vitamin D has a significant reduction in bone re-absorption and formation compared with 25(OH)D (Miheller et al., 2009). Each 100 IU/day of vitamin D intake from diet and supplements decreases the risk of CD activity by 7% (Ananthakrishnan et al., 2012). In a small cohort of CD patients, vitamin D_3 supplementation with up to 5,000 IU/d for 24 weeks significantly elevated plasma $25(OH)D_3$ from 16 ± 10 ng/ml to 45 ± 19 ng/ml, decreased CDAI scores from 230 ± 74 to 118 ± 66, and improved quality of life scores (Yang et al., 2013b). A study examined the changes in monocyte-derived DC (mo-DC) maturation marker expression and cytokine production in CD

patients who received calcium 1,200 IU (placebo) or vitamin D_3 (1,200 IU) and calcium (1,200mg/d) for 26 weeks. Lipopolysaccharide-matured mo-DC decreased the expression and cytokine production, including IL-10, IL-6, and IL- 1β (Bartels et al., 2014). Sufficient vitamin D levels raise the response of anti-inflammatory cytokine to muscular injury (Barker et al., 2014).

Boothe, Lakehomer, Jacob, Scherl, and Bosworth (2011) presented a study at the American College of Gastroenterology annual meeting in 2011 that examined whether high doses of vitamin D_3 in CD patients with vitamin D deficiency led to increased clinical outcomes. Patients were randomized to receive either 1,000 IU/d or 10,000 IU/d. After 26 weeks of treatment, HBI scores in the group with high vitamin D doses had a significant change compared with baseline (3.25 ± 2.2, 4.8 ± 1.7). Vitamin D levels were significant when comparing baseline (54.4±22.8) after 26 week (64.2 ± 29.8). The low-dose group had no significant difference. As shown above, 10,000 IU/d of vitamin D_3 supplementation was an effective treatment for improving symptoms of CD (Boothe et al., 2011).

Crohn's patients have lower levels of vitamin, which lead to increased disease activity. The previous studies show vitamin D supplementation significantly increases plasma 25(OH)D in CD patients, but this depends on vitamin D doses. In addition, vitamin D treatment decreases the disease activity levels and improve quality of life scores.

CHAPTER 3

3. METHODOLOGY

3.1 Study phase I

3.1.1 Design and Setting

The phase I study was designed as a double-blind randomized trial of approximately 60 active patients with Crohn's disease who are receiving induction therapy. We performed randomization and blinding of the samples at the Royal University Hospital, University of Saskatchewan. The sample size calculation included patients in Saskatoon, Saskatchewan, Canada, and Riyadh, Saudi Arabia. The study was conducted between October 2013 and September 2014, and our goal was to recruit 30 patients at each site. The patients were divided in three groups to receive different oral doses of vitamin D: Group 1 received vitamin D at 400/d IU (EAR level), group 2 received vitamin D at 2,000 IU daily, and group 3 received vitamin D at 10,000 IU daily. The vitamin D intervention lasted 9 weeks, and data were collected at baseline (0), 9 weeks, and at a 2-month follow-up. The inclusion criteria included participants that have active Crohn's disease (define by biomarker indicators) without any bowel damage, 16–40 years old.

***Exclusion Criteria**:*

1. Patients in remission.
2. Patients who are taking Corticosteroids.
3. Patients who have serum creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), parathyroid hormone (PTH), calcium, or alkaline phosphatase greater than 1.5 times the upper limit of normal at the screening visit.
4. Patients who:

a. Are pregnant

b. Suffer from liver or kidney failure

c. Are unable to take oral supplements or medicine

d. Are known to have hypersensitivity to vitamin D or any of its analogues or derivatives

5. Patients who are suffering from

a. Hypercalcemia

b. Malabsorption syndrome

c. Abnormal sensitivity to the toxic effects of Vitamin D

d. Hypervitaminosis D

3.1.2 Data Collection Strategies

We used several strategies to recruit patients at both sites. We invited participants to participate through posters posted at the Royal University Hospital and followed by face-to-face or phone communication through the inflammatory bowel disease (IBD) clinic at RUH in Saskatoon, SK, Canada and the Internal Medicine Department at King Khalid University Hospital in Riyadh, Saudi Arabia (Appendix 9). In Saskatoon, we asked patients who were interested in participating in the study to make the first appointment with the research assistant. In Riyadh, we recruited participants from an outpatient clinic when they had their follow-up appointments with our IBD team members. Prior to the collection of any information or test, the patient signed the consent form (Appendix 3). We gave the patients subject codes and randomly assigned which level of vitamin D supplementation they would receive. We used the subject codes on all data collection forms to maintain anonymity. Only information relevant to Crohn's disease was recorded from participants' files. We indicated this in the consent form.

We took the participants' anthropometric measurements, including height and weight, laboratory examinations of vitamin D status, and disease activity. Participants completed six 24-hour dietary recalls; the first three recalls were collected at baseline (first 3 weeks) to assess their usual intake, and the other set of recalls were collected at week 9. The other appointments were scheduled at 9 weeks and 2 months after baseline data collected. The research project funding was from the Saudi Arabian Culture Bureau in Canada. The participants' names and contact information were kept confidential, and only research co-investigators accessed them. Each participant had a unique code, which was not identifiable by anyone outside of the research team. All data were stored in a lockable filing cabinet in the principle investigator's office or in a secure network file for up to 5 years (Appendixes 4,5,6,7 and 10).

Table 3.1 Assessment Methods.

Assessments methods	**Timing**		
	Baseline	**End of Intervention**	**Follow-up**
Socio-Demographics questionnaire	✓	-	-
Physical activity questionnaire	✓	-	-
Health Related Quality of Life	✓	-	✓
Dietary assessment 24-hour dietary recalls	✓	✓	-
Laboratory test (WBC, HGB, Hct, platelet, ferritin, vitamin D, hsCRP, fecal calprotectin)	✓	✓	✓
Crohn's disease activity index	✓	✓	✓

3.1.3 Pre-study Screening and Baseline Evaluation.

1. We screened the potential participants based on inclusion and exclusion criteria.

2. In addition to collecting socio-demographic data, we measured vitamin D status and markers of disease activity as the baseline.

3. We completed standard lab tests at baseline and at safety monitoring time (at week 5 and 9) during the trial treatment periods:

   a. Serum: AST, ALT, BUN, Creatinine, 25-hydroxyvitamin D, albumin, calcium, alkaline phosphate, glomerular filtration rate (GFR, calculated value from serum creatinine).

   b. Urine: calcium, creatinine, urinalysis for hematuria.

   c. Parathyroid hormone (PTH) levels, electrocardiography (ECG).

3.1.4 Concomitant medication. During the trial, patients continued to receive their regular treatment for Crohn's disease, which may vary from patient to patient.

3.1.5 Rescue medication and risk management. Patients visited the IBD clinic where they received their treatment. Any issue related to the disease was addressed by the medical team, including the co-investigators. No adverse events are reported for vitamin D at the doses set in the study. However, we regularly checked the patients for any possibility of hypercalcemia, which is the main adverse event relate to vitamin D intake.

Table 3.2 Safety Measurements.

Measurement	Frequency	Timing		
		Baseline (Week 1)	Midpoint Intervention (Week 5)	End of Intervention period (Week 9)
Calcium	3 times	✓	✓	✓
Phosphate	3 times	✓	✓	✓
25(OH)D	3 times	✓	✓	✓
ALT, AST, BUN levels	3 times	✓	✓	✓
Magnesium	3 times	✓	✓	✓
Pregnancy test	1 time	✓	-	-
Creatinine	3 times	✓	✓	✓
Albumin	3 times	✓	✓	✓
GFR	3 times	✓	✓	✓
Urinalysis for hematuria	3 times	✓	✓	✓
PTH	3 times	✓	✓	✓
ECG	3 times	✓	✓	✓

3.1.6 Measurements

3.1.6.1 Demographics and socio-economic status. We collected socio-demographic information using a modified version of the socio-economic and demographic questionnaire from Canadian Community Health Survey (CCHS) 2008. The questionnaire allowed for comparisons with other data sets, including socio-economic information for patients with Crohn's disease in Canada. We used the same questionnaire and income level in Saudi Arabia. We collected information on patient's age and sex, region of origin, education, level of income and income resources, and we

summarized it in four categories using eighteen questions. Table 3.3 shows that household income was defined by total income and number of people residing in the home.

Table 3.3 Household Income.

Number of people in household	**Lowest income level**	**Lower-middle income level**	**Upper-middle income level**	**Highest income**
1 to 2	< $15,000	$15,000- $29,999	$30,000- $59,999	≥ $60,000
3 to 4	< $20,000	$20,000- $39,999	$40,000- $79,999	≥ $80,000
5 and more	< $30,000	$30,000- $59,999	$60,000- $79,999	≥ $80,000

* Household income was defined by total income and number of people residing in the home
Note. (Statistic of Canada, 2008) "Community Health Survey cycle 2.2 (2004)".

3.1.6.2 Dietary assessment. Three 24-hour dietary recalls were collected twice from each patient at the baseline and at the end of the intervention. The first 24-hour dietary recall obtained a patient's exact food intake, while the average dietary intake from the three 24-hour dietary recalls that we collected on different days of the week, each a few days apart, allowed us to estimate the patient's usual intake (Gibson, 2005). We conducted the first 24-hour dietary recall in person on the day of measurement, while we administered the following five 24-hour dietary recalls over the phone or in-person, based on the patient's convenience. The 24-hour recall was conducted by a nutrition research assistant using the USDA Food Models for Estimating Portions. We used a multiple-staged approach for the recalls. First, we asked the patients to report all food and beverages consumed in the last 24 hours without interruption. Next, we asked the patients about foods they may have forgotten, such as snacks. We then asked the patients for detailed information about time, occasion, and portion size, using food models. Then we reviewed the recall with the patient to ensure that no food or beverages were forgotten. Finally, we had the

patients report any supplements they consumed, with specific brand and amount (Conway, Ingwersen, & Moshfegh, 2004; Conway, Ingwersen, Vinyard, & Moshfegh, 2003).

We entered the information that we gathered into the diet analysis program (Food Processor Nutrition and Fitness Software version 10, produced by Esha Research) to obtain each patient's intake of food groups and specific nutrients. This program contains more than 4,000 Canadian food items, and the nutrient values correspond to the Canadian Nutrient File created by Health Canada. If the appropriate food were not in the list, we chose the American food items nearest to it in nutrient content. In Saudi Arabia, we broke recipes down to basic foods before we entered the data into the food processor.

We exported the data to Excel spreadsheets for each participant, and we averaged the three recalls to obtain the patient's usual intake. We examined the results to determine if all of the patients in the study met the Eating Well with Canada's Food Guide recommended servings for vegetables and fruits, dark green and orange vegetables, grain products, meat and alternatives, and milk and alternatives. We did this by comparing the amount of servings per day to the Eating Well with Canada's Food Guide. The patients' dietary intakes of energy, calcium, zinc, iron, sodium, and vitamins (D, B6, and B12) were analyzed in exactly the same way. We followed a similar approach for Saudi Arabian participants.

We used the Canadian version of the Healthy Eating Index (HEI) to assess the quality of the patients' overall diet. The HEI was originally established by the United States Department of Agriculture (USDA), using a score of the sum of 10 dietary components, with a maximum of 100. Each component of the index has 0 to 10 scores and was adapted according to Eating Well with Canada's Food Guide (CDC, 2010; USDA, 2013). The components are total grain, whole fruit, vegetable and fruit, dark green and orange vegetables, meat and alternatives, milk and alternatives, saturated and unsaturated fat intake, sodium, and other food. The scoring points for

each component are based on age and sex recommendations from Eating Well with Canada's Food Guide (Garriguet, 2009). The HEI assesses the quality of the diet and gives a score according to three categories: <50= poor diet, 50–80 = needs improvement, and > 80 = good diet (CDC, 2010).

3.1.6.3 Health status. Anthropometric measurements included height, weight, body mass index (BMI), and waist circumference at baseline. We used an electronic scale after calibrated to measure patients' weight in kilograms, and recorded the measurement to the nearest 100 gram for weight. We used a stadiometer with a sliding head plate to measure the patients' height. The participants removed their shoes and any bulky clothing and then stepped on the platform and stretched their backs as much as possible. We recorded the readings in centimetres to the nearest millimetre.

Body mass index (BMI) is calculated using the height and weight for each patient. BMI is identified as weight divided by height squared (kg/m^2). We assessed the body mass index of each patient according to World Health Organization (WHO) classifications: <18.5 underweight, 18.5–24.9 normal, ≥ 25 overweight, and ≥ 30 obese (WHO, 2014). We evaluated each patient's waist circumference to the closest 0.1 cm with the patient in the standing position, using a steel flexible tape around the patient's abdomen at the highest point (the iliac crest) at minimal respiration (Li, Ford, Mokdad, & Cook, 2006). We calculated the waist to height ratio by using height and waist circumference.

We evaluated the patients' general physical activities by using the Canadian Health Measures Survey Cycle 2 Physical Activity Questionnaire, 2011. The questionnaire included six questions related to leisure activity and time spent on physical activity at work. It was a recall for past 3 months that defines physical activity to be any activity that was done during past 3 months (Statistic of Canada, 2012). To determine the patient's activity level, we calculated the physical

activity index by the energy expenditure (EE) for each activity, which is expressed by multiplying the average duration of each activity (in hours) expended in leisure time (D), the metabolic equivalent value (MET) for each activity (kcal/kg/d), and the number of times the individual participated in each activity. We then divided the value by number of days in 3 months (91 days). Then we estimated the physical activity index by summing the EE for each activity. We categorized individuals based on PAI values: inactive < 1.5 kcal/kg/d, moderately active 1.5 to <3 kcal/kg/d, and active ≥3 kcal/kg/d (CCHS, 2004).

We used the Health-Related Quality of Life (HRQOL) or IBD questionnaire from the McMaster Industry Liaison office at McMaster University to evaluate the health-related quality of life for patients with IBD. This questionnaire is validated and a reliable tool to measure HRQOL in adults with IBD. It is a self-administrated version and consists of 32 questions classified into four dimensions: bowel, social, systemic, and emotional. This questionnaire is recall over the last 2 weeks. A score of 1 indicates the poorest condition and a score of 7 indicates the best condition (Flintbox, 2010).

3.1.6.4 Disease biomarkers and vitamin D levels. We used different indicators to evaluate the disease activity in patients with CD. Biomarkers of disease activity include C-reactive protein and fecal Calprotectin and inflammation, such as complete blood count and albumin. A subjective tool, Crohn's disease activity index (CDAI) was used to estimate the patient's disease activity. Personnel in the laboratory at each hospital site determined serum vitamin D levels measuring 25-hydroxyvitamin D levels. They measured the patients at the beginning of the study, after 9 weeks, and 2 months from week 9. We then compared the results to the optimal level that is required (Appendix Table 3.4).

3.1.7 Data Analysis

We summarized data in tables at three different points in time. We were unable to conduct a descriptive analysis because of the small sample size that we had. We then presented the results as a case series.

3.1.8 Efficacy Variables and Analysis

1. Primary outcome: We examined the changes in disease activity in patients in the different groups that received three different doses of vitamin D. The disease activity indicators are Calprotectin, hsCRP and CDAI.

2. Secondary outcomes: nutritional status determined by using 24-hour dietary recall, and health-related quality of life, which were determined by inflammatory bowel disease questionnaire (IBDQ), respectively. This questionnaire was purchased from the website FLINTBOX (Flintbox, 2010).

3.1.9 Premature Withdrawal/Discontinuation Criteria

1. Voluntary withdrawal
2. Any indication of potential adverse event due to the intervention
3. Major health issues related to Crohn's disease, such as surgery, which may make continuous enrolment in the study challenging
4. Pregnant women are excluded from our study. We test for pregnancy at the baseline to ensure that none of the female participants were pregnant. If a female participant becomes pregnant, she should be withdrawn from the study, as indicated in the consent form.

3.1.10 Safety Variables and Analysis

We did not face any adverse events related to vitamin D in the described doses. However, to avoid hypercalcemia as the main potential adverse event, in addition to monitoring the relevant symptoms, we collected blood vitamin D status, total serum calcium corrected for albumin level,

blood urea nitrogen, and creatinine concentrations (renal function) at the baseline, mid-point, and end of the intervention week 9.

3.1.11 Ethics

We obtained ethics approval from University of Saskatchewan Research Ethics Board (Bio# 13-180) in August 2013 and we extended the study to 1 year, with an ethics date of July 2014. Health Canada approved the therapeutic products directorate in August 2013, and Saskatoon Health Region gave university ethics approval in March 2014. The College of Medicine at King Saud University and King Khalid University Hospital in Riyadh, Saudi Arabia, approved the ethics documents (Bio13-1048) in February 2014. We completed the certificate of training biosafety, laboratory safety, and (TCPS 2: CORE) tri-council policy statement "Ethical conduct for research involving humans" at the University of Saskatchewan in 2013. (Appendix 8)

We faced many obstacles in recruiting participants at each site, including a small number of initial participants, as well as participants who withdrew, and participants who were missing during the follow-up. Over a year, there was a small number of patients (n=11) who participated in the study (Saskatoon (n=3) and Riyadh (n=8)). Due to the small sample size, we present the results of study phase I as a case series. We decided to conduct a retrospective cohort study called study phase II to determine the association of vitamin D and disease activity in patients with CD.

3.2 Study Phase II

3.2.1 Design, Study Site, Data Source, and Ethics Approval

This phase contains a retrospective cohort study of approximately 201 patients with Crohn's disease. We extracted the data from medical charts at the IBD clinic of the Royal University Hospital in Saskatoon, Saskatchewan, Canada. The study objective was to determine the association between vitamin D status and disease activity in a cohort of patients with CD. The biomedical research ethics board (#Bio 14-161) at the University of Saskatchewan and the

Saskatoon Health Region approved the ethics documents during the summer of 2014. I completed a McMaster Certificate of Completion for completing the tutorial for researchers conducting a retrospective review of health records in June 2014.

3.2.2 Data Collection Strategies

We requested username and password to access the medical charts at Royal University Hospital. We collected the data from July to August 2014 and entered them directly into a password-protected Excel spreadsheet. We then stored the data collection file in a university network JADE file for Dr. Vatanparast. The data items include age, sex, disease duration, current medications and supplements, history of surgery, Harvey-Bradshaw Index (HBI) scores, and blood test (e.g. hsCRP and 25(OH)D). The season of measurements was also taken into account. I extracted all available data and entered them into the excel spreadsheet, and then divided into three different points in time (first visit, midtime visit, last visit). We describe specific details about the variables used in Table 3.5.

Table 3.5 Variables Used in the Data Analysis.

Variable	Type	Description
Age	Continues	At each time points
Sex	Categorical	Male , female
Disease duration	Continues	Duration of CD from the day of diagnosed
Times	Categorical	Time 1 = first visit , Time 2= 8 months (mean of number of months from the first visit), Time 3= last visit
months	Continues	Number of months from the first visit
HBI score	Continues/ Categorical	1. Remission < 5 2. Active disease ≥ 5
History of surgery	Categorical	Yes , No
hsCRP level	Continues/ Categorical	1. low risk <1 2. Intermediate risk between 1-3 3. High risk > 3
25(OH)D level	Categorical	1. Vit D deficient <29 nmol/L 2. Vit D insufficient 29-50 nmol/L 3. Vit D Adequate 51-74 nmol/L 4. Vit D Optimal >75 nmol/L
Vitamin D supplementation	Continues	Amount of vitamin D doses
Season	Categorical	1. April to Sep 2. Oct to Mar
Corticosteroid drugs use	Categorical	Yes , No

3.2.3 Statistical Analysis

We used descriptive statistics to summarize the data as means and standard deviation (SD) for continued variables and percentages for categorical variables at three time points. I completed the descriptive analysis using SPSS Version 22 (IBM 2014). We conducted a non-parametric test Kruskal-wallis post hoc to test the significance of variables between time points and know which group differ from other. For analytical analysis, we used generalized estimating equations (GEE). GEE is a convenient approach to estimate the possible unknown correlation and

changes between outcomes over time that have an impact on covariates (Liang & Zeger, 1986). This test includes all available data (completed and missing data) in an unbalanced design; it is more efficient and has a higher power with a smaller sample size or lower number of repeated measurements ANOVA (Ma, Mazumdar, & Memtsoudis, 2012). Since the long forms of the data were being used, only observations that have missing subjects are lost, not all measurements (Twisk, 2013).

In this current study, the exchangeable correlation matrix between hsCRP, the main factor serum vitamin D, and several predictors were evaluated by GEE at three time points of measurements. The predictors for HBI score and hsCRP were age, sex, three of the measurements, vitamin D level, disease duration, use of corticosteroid, surgery, and season. Analytical analyses were conducted by STATA/SE 11; StataCorp and alpha was set at 0.05. We used GEE exchangeable correlation matrix with a hsCRP variable using the following model: (xtgee hscrp age sex disease_duration i. times surgary i. vitd_cat4 cs season, family(gaussian) link(identity) corr(exchangeable) eform). To evaluate the association between vitamin D and HBI in presence of other covariates, GEE with logistic regression was used with cut-off HBI score as categorical variable using the following model: (xtgee hbi_2cat age sex disease_duration i. times surgary i. vitd_cat4 cs season, family(binomial 1) link(logit) corr(exchangeable) eform).

CHAPTER 4

4 RESULTS

4.2 Study Phase I (Case Series)

4.1.1 Subject Characteristics

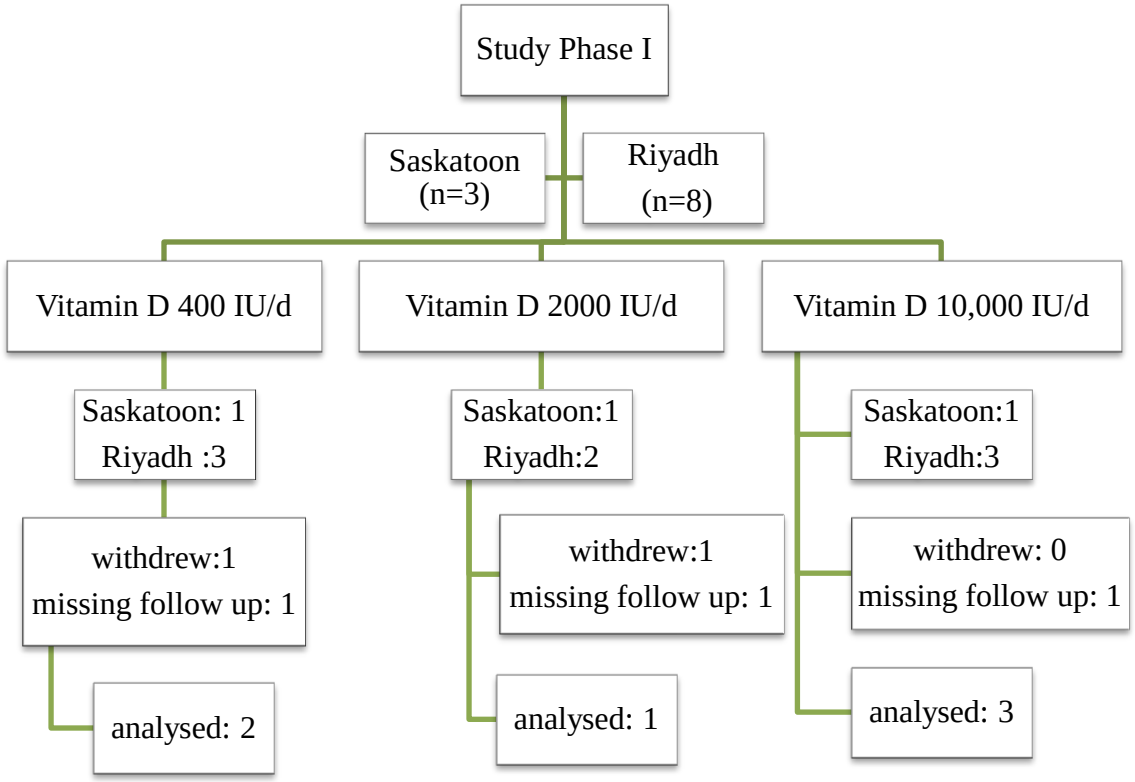
We recruited 11 adults from Royal University Hospital in Saskatoon and King Khalid University Hospital in Riyadh. We deemed these subjects eligible to participate in the study. Two subjects had withdrawn themselves on the first day of the study and thus are not included. One further subject had lung cancer and withdrew during the follow-up. Two subjects were missing from the follow-up. The following results are presented for nine participants, six from Saudi Arabia and three from Saskatoon. Figure 4.1 study design.

Socio-demographic data are presented for nine patients. Their age was ranged from 19 to 60 years old, five males and four females. All participants were educated except for one case from Saskatoon. Saudis' participants were Arab and Canadian participants were Caucasian. Case 5 from Saskatoon had upper-middle income level according to Statistic Canada income categories (Statistic of Canada, 2008). Three participants from Saudi had lowest income level and one had lower- middle-income category according to Statistic Canada, 2008 Appendix table 4.1 presented Socio-demographic characteristics.

In general, among nine participants, four patients had normal weight, three patients were underweight, and two were overweight. Physical activity index indicates that eight patients have sedentary lifestyle and only one patient was moderately active. Health-related quality of life was improved in three patients comparing the score at baseline and at followup. According to Healthy Eating Index Canada (HEI), at baseline, six patients had poor diet and three patients needed improvement in their diet. At week 9 (end of intervention), four patients had poor diet, four

patients needed improvement and one patient missed follow up. Comparing both time points, HEI was improved in two patients. Vitamin D status and related information are presented in Table 4.2 .Table 4.5 shows intake of food groups and HEI.

Figure 4.1 Study design



4.1.2 Vitamin D and disease status

Tables 4.2 and 4.3 provide information on vitamin D status and disease activity throughout the study. Among the group who were receiving vitamin D with the dose of 400 IU/day, two patients had vitamin D deficiency and two patients had vitamin D insufficiency at the baseline. Vitamin D levels were improved at week 9, however declined at follow-up. The hsCRP levels were decreased in three patients while five patients had increased hsCRP levels at week 9 with concurrent changes in other factors such as medication, dietary intake and physical activity. In addition, vitamin D deficiency can concurrently be seen with high disease activity

level; however, high level of vitamin D supplementation coincides with decreased hs-CRP level. In one case with available Calprotectin level, it decreased significantly from baseline to week 9, while vitamin D status increased rapidly from 36.6 to 105.5 nmol/L. There was only one patient who received 2000 IU of vitamin D. Her vitamin D level was raised over time while hsCRP level decreased in followup. Patients who received 10,000 IU of vitamin D had considerable increase in vitamin D levels in week 9, which decreased at followup. However, hsCRP levels were slightly increased in week 9 and followup; only one case had decreased hsCRP level at the follow-up. Appendix tables 4.7, 4.8, 4.9 and 4.10 present laboratory and safety measurements at four time points. Table 4.4 presents Average Dietary Usual Intake of Nutrients Associated with IBD at Baseline and Week 9 comparing to RDA

4.1.3 Case Reports

4.1.3.1 Case 1. Case 1 was a 60-year-old female with active CD. She was in the diagnosis process of hyperthyroidism. No current medication was in place. She was taking a probiotic and was assigned to receive 400 IU/d of vitamin D_3. We completed baseline measurements during the first week of the study and week 9 lab tests with a 2-week delay (week 11). She was overweight with moderate physical activity, and her HEI was in the needs improvement category. Her hsCRP results were 8.1 mgs/L at baseline and 40.7 mgs/L at week 11, indicating high disease in disease activity levels over time. HBI and CDAI were not accurate indicators to estimate the disease activity; both indicated inactive disease (remission), and HBI indicated moderate disease at week 11. Although she was exposed to sunlight 1 to 2 hours daily, she had an insufficient vitamin D level (36.6 nmol/L) at baseline. After receiving vitamin D treatment with a dose of 400 IU per day, her vitamin D level increased from 36.6 to 105.5 nmol/L. In addition, her vitamin D intake from food increased from 122.1 to 4047.2 IU. During her follow-up, Case 1 asked the research coordinator if she could withdraw from the study because she was diagnosed with stage IV lung

cancer. Due to the lung cancer, the research coordinator advised Case 1 to withdraw from the study.

4.1.3.2 Case 2. Case 2 was a 25-year-old male with active CD. He had a bachelor's degree, and his main source of income was wages at the lowest income level. The disease was located in the small bowel (jejunum) and colon (ascending, transverse, descending, and sigmoid). The CD was controlled by 5-ASA and Azathioprine. We assigned him to receive 400 IU/d of vitamin D_3. We completed baseline measurements during the first week of the study, the week 9 lab tests with a 2-week delay (week 11), and the 2-months follow-up with a 4-month delay (6 months from week 11). He was an inactive person with a normal BMI, and his HEI was in the poor diet category at baseline and then the needs improvement category at week 11. His HRQOL score was 200 at baseline and 197 at the follow-up, which indicated good or same level quality of life. His hsCRP results were 5.8 mgs/L at baseline, 4.9 mgs/L at week 11, and 0.7 mgs/L at the follow-up, indicating a decrease in the disease activity levels over time. HBI and CDAI were not accurate indicators to estimate the disease activity. HBI indicated mild disease at baseline and remission at the follow-up. Although he was exposed to sunlight 1 to 2 hours daily, he had an insufficient vitamin D level (33.0 nmol/L) at baseline. After receiving vitamin D treatment with a dose of 400 IU per day, his vitamin D level increased from 33.0 to 59.0 nmol/L at week 11. Then his vitamin D decreased to 42.5 nmol/L at the follow-up. In addition, his vitamin D level from food improved from 30.2 to 58.9 IU.

4.1.3.3 Case 3. Case 3 was a 21-year-old female with mild to moderate CD. She had a bachelor's degree and the lowest income level. The CD location was in the small bowel and colon (ascending, transverse, descending, and rectum). Her doctor placed her on Azathioprine and Adalimumab. We assigned her to receive 400 IU/d of vitamin D_3. We completed her baseline measurements during the first week of the study, the week 9 lab tests at a 2-week delay (week

11), and the 2-month follow-up with a 4-month delay (6 months from week 11). She was underweight and inactive, and her HEI was in the poor diet category. The HRQOL score decreased from 183 at baseline to 152 at follow-up, which indicates a worse quality of life. Her hsCRP results increased from 11.6 mgs/L at baseline, 11.8 mgs/L at week 11, and 19.5 mgs/L at follow-up. However, her vitamin D level increased from 8.8 to 14.5 nmol/L at week 11 and then decreased to 9.8 nmol/L at the follow-up. Vitamin D from food increased from 22.1 to 92.5 IU. She was exposed to sunlight for less than 30 minutes daily.

4.1.3.4 Case 4. Case 4 was a 19-year-old female high school student. She was taking Azathioprine drugs and had a perianal fistula. We assigned her to receive 400 IU/d of vitamin D_3. We completed her baseline measurements and week 9 lab test on time. She was underweight with inactive physical activity, and her HEI was in the poor diet category. The hsCRP results were 10.1 mgs/L at baseline and 8.5 mgs/L at week 9, indicating low disease activity levels over time. She was exposed to sunlight < 30 minutes daily, and she had deficient vitamin D levels (12.8 nmol/L) at baseline. After receiving vitamin D treatment with a dose of 400 IU per day, her vitamin D level increased from 12.8 to 36.9 nmol/L. The research coordinator tried to keep in touch with Case 4 but she was lost during the follow-up.

4.1.3.5 Case 5. Case 5 was a 32-year-old female. Her highest grade of education was below grade 8, her main source of income was wages, and she was in the upper middle-income level. The CD location was in the small bowel (terminal ileum and ileocecal valve) and colon (cecum, ascending, transverse, descending, and sigmoid). Her doctor placed her on Budesonide, and she was taking multivitamins. We assigned her to receive 2000 IU/d of vitamin D_3. We completed her baseline measurements during the first week of the study, the week 9 lab tests with a 5-week delay (week 14), and the 2-month follow-up. She was inactive and overweight, and her HEI was in the needs improvement category. The HRQOL score improved from 178 at baseline to 191 at

follow-up, which indicates a better quality of life. Her hsCRP results decreased from 12.4 mgs/L at baseline, 4.6 mgs/L at week 14, and 0.7 mgs/L at the follow-up. In addition, her vitamin D level steady increased from 63.0 to 73.0 nmol/L at week 14 and 89.0 nmol/L at the follow-up. Vitamin D from food decreased from 988.6 to 829.4 IU. She was exposed to sunlight for 2 to 3 hours daily and used sunscreen sometimes. Her Calprotectin measurement levels were 1.99 mg at baseline and 1.37 mg at follow-up, which indicated that the inflammation decreased.

4.1.3.6 Case 6. Case 6 was a 35-year-old male with mild active CD in the small bowel (terminal ileum and ileocecal valve) and colon (cecum, ascending, transverse, descending, sigmoid). He was treated with Azathioprine and then Budesonide. We assigned him to receive 10,000 IU/d of vitamin D_3. We completed baseline measurements during the first week and week 9 with a 4-week delay (week 13). His weight was normal, he had inactive physical activity, and his HEI was in the poor diet category at baseline and the needs improvement category at week 14. His hsCRP results were 4 mgs/L at baseline and 5.7 mgs/L at week 9, indicating high disease activity levels over time. He was exposed to sunlight for 3 to 4 hours daily, and he had deficient vitamin D levels (18.6 nmol/L) at baseline. After he received vitamin D treatment with a dose of 10,000 IU per day, his vitamin D level increased from 18.6 to 78.0 nmol/L. His vitamin D from food improved from 137.4 to 187.2 at week 13. The research coordinator tried to communicate with him several times but he was lost during the follow-up.

4.1.3.7 Case 7. Case 7 was a 25-year-old male with active CD in the small bowel (terminal ileum) with perianal abscess. His income was based on wages, and he was in the lowest income category. He was an educated person with bachelor's degree. The CD was treated with Infliximab. We assigned him to receive 10,000 IU/d of vitamin D_3. We completed his baseline in the first week and week 9 lab tests with 1-week delay (week 10) and the 2-month follow-up with a 4-month delay (6 months from week 10). He was an inactive person with a normal BMI. His

HEI indicated that his diet was in the poor diet category. His HRQOL score improved from 159 to 188 at the follow-up, which indicates a better quality of life. C-reactive protein levels remained the same: 1.2 mgs/L at baseline, 1.2 mgs/L at week 10, and 1.4 mgs/L at follow-up. He lost his vitamin D supplements (2 weeks with no vitamin D), and then he asked the research coordinator if he could have another bottle. He had vitamin D deficiency (27.3 nmol/L) at the baseline, and his vitamin D level increased significantly to 164.9 nmol/L at week 10. Then his vitamin D decreased to 120 nmol/L at the follow-up. In addition, his vitamin D level from food improved from 46.2 to 78.5 IU.

4.1.3.8 Case 8. Case 8 was a 28-year-old male with active CD in the small bowel and colon (sigmoid, rectum). He was an educated person with a bachelor's degree, his main income was wages, and he was in the lower middle-income level. His doctor prescribed Azathioprine and Adalimumab and he was taking multivitamins. He received 10,000 IU/d of vitamin D_3. We completed his baseline in the first week and week 9 lab tests with a 6-week delay (week 15), and the 2-month follow-up with a 2-week delay. He was an inactive person with a normal BMI. The HEI indicated that his diet was in the poor diet category. His HRQOL score decreased from 218 to 203 at follow-up, which indicated a worse quality of life. C-reactive protein levels were 0.53 mgs/L at baseline and 0.9 mgs/L at week 15, and this increased significantly to 19.8 mgs/L at the follow-up. He had an optimal vitamin D level (87.6 nmol/L) at baseline and his vitamin D level increased significantly to 138.1 nmol/L at week 15. At the follow-up, vitamin D decreased to 88.0 nmol/L. His vitamin D level from food was 53.1 IU at baseline and 45.7 IU at week 15. Case 8 was exposed to sunlight for less than 30 minutes daily, and sometimes he used sunscreen to protect his skin from the strong sunlight.

4.1.3.9 Case 9. Case 9 was a 24-year-old male with active CD in the small bowel and terminal ileum. His income level was upper middle-income level, his income was based on wages, and he

was an educated person with a bachelor's degree. He was treated with Azathioprine. He received a high dose of vitamin D_3 10,000 IU/d. We completed week 9 measurements on time and follow-up measurements with a 47-day delay. He was an underweight and inactive person, and his HEI showed that his diet was in the poor diet category. Quality of life increased from 161 to 206 at follow-up, which indicates a better quality of life. C-reactive protein levels were 12.9 mgs/L at baseline, increased in week 9 to 22.8 mgs/L, then decreased significantly to 5.9 mgs/L at follow-up. He had an optimal vitamin D level (77.9 nmol/L) at baseline and 88.4 nmol/L at week 9. During the follow-up, vitamin D decreased to 67.6 nmol/L. His vitamin D level from food was 59.9 IU at baseline and 123.5 IU at week 9. Case 9 was exposed to sunlight from 1 to less than 2 hours daily.

Table 4.2 Vitamin D Status as 25-hydroxyvitamin D levels and Related Info.

Case	Supplement use	Exposure to sunlight	Use of sunscreen	Vitamin D treatment group (IU)	Baseline	Week 9	Follow-up
					25(OH)D (nmol/L)	25(OH)D (nmol/L)	25(OH)D (nmol/L)
Case 1	No	1 to < 2 h	always	400	36.6	105.5	-
Case 2	No	1 to < 2 h	rarely	400	33.0	59.0	42.5
Case 3	No	<30 min	never	400	8.8	14.5	9.8
Case 4	No	<30 min	never	400	12.8	36.9	-
Case 5	multivitamin	2 to < 3 h	sometimes	2000	63.0	73.1	89.0
Case 6	No	3 to < 4 h	rarely	10,000	18.6	78.1	-
Case 7	No	None	sometimes	10,000	27.3	164.9	120
Case 8	multivitamin	<30 min	sometimes	10,000	87.6	138.1	88.1
Case 9	No	1 to < 2 h	sometimes	10,000	77.9	88.42	67.6

Table 4.3 Disease Activity Lab Measurements and Indicators throughout the Study.

Case	Baseline					Week 9				Followup				
	HBI	CDAI	HRQOL	hsCRP (mgs/L)	Calprotectin (mg)	HBI	CDAI	hsCRP (mgs/L)	Calprotectin (mg)	HBI	CDAI	HRQOL	hsCRP (mgs/L)	Calprotectin (mg)
Case 1	0	41	145	8.1	6.39	8	76.6	40.7	1.3	-	-	-	-	-
Case 2	6	88.2	200	5.8	-	3	67.6	4.9	-	3	111.9	197	0.7	-
Case 3	8	111.2	183	11.6	-	5	73.2	11.8	-	2	82.2	152	19.5	-
Case 4	0	101.4	190	10.1	-	3	102.4	8.5	-	-	-	-	-	-
Case 5	2	130	178	12.4	1.99	3	130	4.6	-	0	50	191	0.7	1.4
Case 6	7	89.2	153	4	2.47	2	47	5.7	-	-	-	-	-	-
Case 7	2	61.2	159	1.2	-	2	49.2	1.2	-	2	61.2	188	1.4	-
Case 8	1	50	218	0.5	-	0	50	0.9	-	1	69.1	203	19.8	-
Case 9	2	39	161	12.9	-	11	39.5	22.8	-	2	39.5	206	5.9	-

* HBI (Harvey-Bradshaw Index), CDAI (Crohn’s disease activity index), HRQOL (Health-related quality of life).

Table 4.4 Average Dietary Usual Intake of Nutrients Associated with IBD at Baseline and Week 9 comparing to RDA

Case	Ca (mg) **(1000)****	Fe (mg)	Zinc (mg)	Na(mg) **(1500)***	Vit D** **(600IU)**	Vit C (mg)	Vit E (mg) **(15)****	Vit B6 (mg) **(1.3)****	Vit B12(mcg) **(2.4)****	Sat fats (g)	Unsat fats (g)	Calories
	Baseline (**RDA or AI)**											
	Week 9											
Case 1	612.4	6.6 (**8)**	5.9 (**8)**	1753.6(**1300)**	122.1	57.6 (**75)**	2.9	1.3 (**1.5)**	2.8	11.7	7.9	1042.4
	1607.7	9.4	7.3	2222.9	4047.2	56.5	3.8	1.5	2.3	13.5	14.4	1458.5
Case 2	420.8	11.0 (**8)**	5.6 **(11)**	2204.8	30.2	69.1 (**90)**	1.9	0.6	1.9	29.0	13.3	1708.7
	441.3	6.9	7.5	1135.0	58.9	86.9	2.0	1.1	1.8	10.9	9.8	1401.7
Case 3	431.6	10.6 (**8)**	8.8 (**8)**	2047.7	22.1	0.7 (**75)**	54.7	1.9	1.0	18.1	22.8	1776.3
	344.2	8.0	6.4	3216.0	92.5	55.9	1.0	0.8	3.0	20.1	18.2	1644.1
Case 4	496.9	10.7(**18)**	5.0 (**8)**	2091.8	75.0	14.7 (**75)**	2.2	0.9	1.9	19.9	9.6	1168.6
Case 5	1550.0	21.0(1**8)**	10.7 (**8)**	2163.3	988.6	150.9 (**75)**	8.6	3.6	13.1	33.0	16.3	1964.5
	969.7	16.2	10.5	1406.6	829.4	85.5	12.1	3.9	6.3	17.3	15.6	1504.8
Case 6	998.7	12.7 (**8)**	6.8 **(11)**	3927.3	137.4	120.8 (**90)**	1.8	1.2	2.1	31.9	7.5	1812.1
	796.0	26.7	11.9	3097.5	187.2	6.5	0.8	1.7	4.1	16.4	8.3	1612.0
Case 7	239.9	10.3 (**8)**	12.9**(11)**	2072.5	46.2	79.3 (**90)**	3.7	1.1	3.9	21.7	22.1	2231.6
	453.3	6.3	8.6	1183.2	78.5	10.1	1.6	1.1	3.0	18.2	16.1	1850.5
Case 8	246.9	7.4 (**8)**	7.9 **(11)**	1116.1	53.1	40.7 (**90)**	3.7	1.3	1.4	18.3	13.4	941.1
	375.0	7.9	3.9	2124.7	45.7	47.7	10.3	1.2	0.9	14.7	18.1	1797.9
Case 9	351.9	7.1 (**8)**	5.4 **(11)**	1482.4	59.9	4.2 (**90)**	1.2	1.0	0.9	12.7	9.3	1306.9
	500.5	7.0	3.6	2942.8	123.5	7.4	0.9	0.6	1.5	11.3	4.7	1104.2

*Average dietary usual intake was derived from the average of 24 hours dietary recalls. *Adequate intake (AI) **RDA
* Nutrients usual intake was comparing with RDA for healthy people from the Institute of Medicine.

4.2 Study Phase II (Retrospective Cohort)

4.2.1 Descriptive Analysis

We present the descriptive results for the retrospective data for (n=201) patients with Crohn's disease at Royal University Hospital, Saskatoon, SK. Canada. Table 4.11 and 4.12 summarize the descriptive characteristics for the retrospective data.

4.2.1.1 Socioeconomic, demographic, disease duration, and surgery and corticosteroids. Table 4.11 shows Sex distribution was 42.3% male and 58.7% female with mean age of 40.2±15.2 y, 40.8±15.2 y and 41.5±15.1 y at three time-points (time 1, time 2, and time 3). The number of months from the first visit was 8.2±5.5 month for the second visit and 15.3±6.6 month for the third visit. Mean of CD duration at the first visit was 9.7 years. History of surgery was reported in 35.8%, 37.3% and 39.4% at three time-points respectively. Only 19.4% patients were placed on corticosteroids in the first visit and 14.3% in the last visit.

Table 4.11 Descriptive Characteristics for the Retrospective Cohort Data Socioeconomic Demographic, Disease Duration, Surgery and Corticosteroids Variables

Variables	**Time 1**	**Time 2**	**Time 3**
Age (y) (n=201)	40.2±15.2	40.8±15.2	41.5±15.1
Sex	*(n=201)*	*(n=201)*	*(n=201)*
Male	83 (41.3)	83 (41.3)	83 (41.3)
Female	118 (58.7)	118 (58.7)	118 (58.7)
Number of months from the first visit (months)	-	8.2±5.5	15.3±6.6
History of surgery	*(n=201)*	*(n=201)*	*(n= 180)*
Yes	72 (35.8)	75(37.3)	71 (39.4)
No	129 (64.2)	126 (62.7)	109 (60.6)
Disease duration (y)	*(n=162)*	*(n=162)*	*(n=139)*
	9.7±9.6	10.5 ±9.6	11.2±9.8
Corticosteroids	*(n=196)*	*(n=196)*	*(n=175)*
Not using corticosteroids	158 (80.6)	162 (82.6)	150 (85.7)
Using corticosteroids	38 (19.4)	34 (17.3)	25 (14.3)

*Age and number of months from the first visit presented as mean ± SD

4.2.1.2 Vitamin D status. The mean serum vitamin D level was significantly different between time1 and time 3 (p= .04). At the baseline measurement, the mean 25-hydroxy vitamin D was 58.2±30.0 nmol/L: twenty-six percent of the patients had optimal levels, 30% had adequate vitamin D, 26% had insufficient levels, and 18% of the patients had a deficient vitamin D status. Vitamin D doses were reported in 48 patients, with a mean of 1629.1±1190.7 IU, and most of them were taking a daily vitamin D supplements up to 1,000 IU as a minimum dose. One hundred and sixteen patients had their serum vitamin D measured between April to September, and eighty-six patients had their measurement between October to March.

At the midpoint measurement (time 2), the mean serum vitamin D status was 60.1±31.2 nmol/L: Thirty-one point three percent had optimal levels, 31.3% patients had insufficient levels, 22.1% patients had adequate levels, and 15.2% of patients were vitamin D deficient. One hundred and seven patients were having their measurements between October to March.

During the final visit, 66 patients had vitamin D results with the mean of 74.5±42.6 nmol/L: Forty-three point nine percent of patients had optimal levels of vitamin D, 24.2% patients had adequate levels, 18.1% patients had insufficient vitamin D levels, and 13.6% patients had vitamin D deficiency. Vitamin D supplements were used by only 47 patients (28.0 %) with the mean intake of 2085.1±1501.1 IU. Most patients had their last visit (114 from 168 CD patients) between April to September.

4.2.1.3 Disease biomarkers (CRP) and HBI scores. The mean of the hsCRP test varied significantly between time 1 and time 3 (p=.001). During the first visit, 192 patients had serum hsCRP with a mean of 13.0± 22.3 mgs/L, and 55.7% of them had high levels of hsCRP. Among patients who reported their HBI scores (n=187); 3.2% had a sever disease, 31% were mild disease, 33.1% had a moderate disease and 32.1% were in remission. During the second visit, 48.2% of patients had very high levels of hsCRP, 30.2% had moderate level and 21.5% had low

levels of hsCRP. The mean of the hsCRP levels decreased significantly (p=.001) from the first visit to the third visit, 13.0± 22.3 mgs/L to 7.2±15.4 mgs/L, respectively. Of the patients tested, 38.6% had high levels of hsCRP at Time 3. Close to half of patients (n=35 from 67 patients) were in remission based on their HBI score. Table 4.12 shows descriptive characteristics for the retrospective cohort data for vitamin d status, dosage and disease activity variables.

Table 4.12 Descriptive Characteristics for the Retrospective Cohort Data for Vitamin D Status, Dosage and Disease Activity Variables

Variables	**Time 1**	**Time 2**	**Time 3**
Serum 25(OH)D status	*(n= 116)*	*(n= 118)*	*(n= 66)*
(nmol/L)	**58.2± 29.9**	60.1± 31.2	**74.5± 42.6**
Vitamin D categories	*(n=116)*	*(n=118)*	*(n=66)*
Deficient	21 (18)	18 (15.2)	9 (13.6)
Insufficient	30 (26)	37 (31.3)	12 (18.1)
Adequate	35 (30)	26 (22.1)	16 (24.2)
Optimal	30 (26)	37 (31.3)	29 (43.9)
Vitamin D doses (IU)	*(n= 48)*	*(n= 56)*	*(n= 47)*
	1629.1±1190.7	2095.3±1860.1	2085.1±1501.2
hsCRP (mgs/L)	*(n= 192)*	*(n= 195)*	*(n= 158)*
	13.0± 22.3	11.2± 28.9	**7.2± 15.4**
hsCRP categories	*(n=192)*	*(n=195)*	*(n=158)*
Low risk	35 (18.2)	42 (21.5)	49 (31)
Intermediate risk	50 (26)	59 (30.2)	48 (30.3)
High risk	107 (55.7)	94 (48.2)	61 (38.6)
HBI score	*(n=187)*	*(n=90)*	*(n=67)*
	7.0±4.4	6.3±4.8	6.0±5.2
HBI score categories	*(n= 187)*	*(n= 90)*	*(n=67)*
Remission	61 (32.6)	40 (44.4)	35 (52.2)
Mild disease	58 (31)	17 (18.8)	10 (14.9)
Moderate disease	62 (33.1)	29 (32.2)	18 (26.8)
Severe disease	6 (3.2)	4 (4.4)	4 (5.9)
Season	*(n=201)*	*(n=201)*	*(n=168)*
April to September	115 (57.2)	94 (46.8)	114 (67.8)
October to March	86 (42.8)	107 (53.2)	54 (32.1)

4.2.2 Results from Statistical Modeling

4.2.2.1 High sensitivity C-reactive protein (hsCRP). Table 4.13 shows the estimates of the model parameters with 95% confidence intervals along with results of the tests for their statistical significance. Out of eight predictor variables included in the model, only three predictors showed statistically significant association with hsCRP level. These statistically significant predictors of hsCRP level were Corticosteroids, time of measurement, and vitamin D categories. Age, sex, disease duration, season, and surgery did not show a statistically significant effect (P > .05) on hsCRP level.

The estimated coefficient for Corticosteroids is Coef. = 7.2 with a 95% confidence interval (1.0, 13.5). Time of visit also showed a significant association with hsCRP. In the last visit, patients showed a significantly lower mean hsCRP level compared to first visit (Coef. = -9.2, p =.013). However, no significant difference in hsCRP level was found between the first visit and the second visit, which was measured approximately 8 months after the first visit. Vitamin D status also showed a significant association with hsCRP level. Vitamin D status was included in the model as a categorical variable: deficient (reference) insufficient, adequate and optimal levels. All the three categories showed significantly lower mean hsCRP level compared to deficient vitamin D category (p <.05). The insufficient vitamin D category had a Coef. = 12.8 units lower, while the adequate vitamin category had a Coef. =7.8 units, and the optimal vitamin D category had a Coef. = 9.8 units of hsCRP level lower compared to the deficient vitamin D category. In summary, the deficient vitamin D category had a significantly higher hsCRP level than all of the other three categories of vitamin D status.

Table 4.13 Factors Associated with hsCRP Levels among Crohn's Disease Patients

hs-CRP continues variable	**Coefficient (Coef.)**	**95% Confidence Interval**	***P-value**
Age (y)	-0.1	(-0.3, 0.1)	0.449
Sex	-4.5	(-11.4, 2.3)	0.194
Disease duration (y)	0.2	(-0.1, 0.6)	0.185
Corticosteroids	**7.2**	**(1.0, 13.5)**	**0.023**
Season	3.7	(-0.6, 8.1)	0.092
Surgery	0.1	(-7.8, 8.2)	0.968
Times			
Time 2	-2.7	(-7.2, 1.6)	0.224
Time 3	**-9.2**	**(-15.1, -3.4)**	**0.002**
Vitamin D categories			
Insufficient	**-12.8**	**(-19.8, -5.8)**	**0.000**
Adequate	**-7.8**	**(-14.9, -0.7)**	**0.031**
Optimal	**-9.8**	**(-17.6, -2.0)**	**0.013**

*P value was determined using GEE test. P<0.05 was considered to be significant.

4.2.2.2 Harvey-Bradshaw Index indicator category (HBI). GEE, binary logistic regression was used to explore possible association between selected predictor variables and likelihood of active disease (cut-off ≥ 5 score). Table 4.14 shows the estimates of odds ratio for each predictor, along with results of the test for their significance. Three predictor variables—(i) use of corticosteroids, (ii) time of visit and (iii) vitamin D status—had a significant effect on the odds of active disease.

The use of corticosteroids had an odds ratio estimate of 5.5. Time of visit was significantly associated with active disease. The second visit, 8 months after the first visit, had an odds ratio of 0.4. This means that the odds of having an active disease during the second visit were 58% lower than odds at the first visit. This odds ratio is found to be statistically significant

(OR = 0.4, p = .025). The last visit had an odds ratio of 0.2. This means that odds of having active disease during the last visit were 71% lower than odds at the first visit (OR = 0.2, p = .014).

Vitamin D status also associated with disease activity. However, only insufficient category was significantly associated with HBI. The insufficient category had an odds ratio estimate of 3.4. For those with vitamin D insufficiency, the odds of having active disease was 3.4 times higher than the reference group (vitamin D deficient) while the vitamin deficient participants had high hsCRP. Adequate and optimal vitamin D status did not report any significant difference in the odds of having an active disease compared to deficient vitamin D status. This indicates the importance of using more objective measure of disease activity in CD patients.

To summarize, statistical analysis of data about high sensitivity C- reactive protein test and HBI categories indicated that the use of corticosteroids, time of visit, and vitamin D status had significant influence on the outcome variables (hsCRP level and HBI Category).

Table 4.14 Factors Associated with HBI Scores among Crohn's Disease Patients

HBI with 2 Categories	**Odds Ratio (OR)**	**95% Confidence Interval**	***P-value**
Age	0.9	(0.9, 1.0)	0.778
Sex	0.7	(0.3, 1.6)	0.505
Disease duration	1.0	(0.9, 1.0)	0.910
Corticosteroids	**5.5**	**(2.1, 14.3)**	**0.000**
Season	0.9	(0.4, 1.9)	0.916
Surgery	0.6	(0.2, 1.6)	0.398
Times			
Time 2	**0.4**	**(0.2, 0.8)**	**0.025**
Time 3	**0.2**	**(0.1, 0.7)**	**0.014**
Vitamin D categories			
Insufficient	**3.4**	**(1.0, 10.8)**	**0.034**
Adequate	1.0	(0.3, 2.9)	0.919
Optimal	2.7	(0.9, 8.2)	0.072

*P value were determined using GEE logistic regression test. P<0.05 were considered to be significant.

- HBI scores with two cut- off categories (0= < 5 remission and 1= ≥5 active disease).

CHAPTER 5

5. DISCUSSION

When this study was designed, there was one unpublished study conducted in the USA to examine the effect of a daily high dose 10,000 IU of vitamin D3 on Crohn's disease patients. To our knowledge, there are only a few published studies that have measured vitamin D levels in CD patients in Canada and Saudi Arabia. There have been no clinical trials in Saudi Arabia that explore the relationship between CD and high dose of vitamin D supplementation. We used different studies to address the research question. Thus the main objectives of this thesis were, first to determine the effect of vitamin D supplementation on disease activity in Crohn's disease patients in Canada and Saudi Arabia. Along with vitamin D, quality of life, socio-demographic and physical activity, vitamin D status, disease biomarkers, and dietary assessment as major determinants of health were examined. Secondly, the association between vitamin D status and disease activity in a cohort of CD patients in Saskatoon, Canada was investigated. This study examined the main outcome disease activity (hs-CRP and HBI) with the main factor "vitamin D status" and other potential predictors such as disease duration, using corticosteroids, surgery, age, sex and diet. All of these factors are discussed in detailed below.

5.1 Vitamin D status, Supplementation

It was hypothesized that patients who are suffering from Crohn's disease are at risk of vitamin D deficiency. In both studies, we reported high rates of vitamin D deficiency/ insufficiency among active CD patients; the prevalence of vitamin D deficiency increased during the winter season. Most phase I cases had vitamin D deficiency/ insufficiency at baseline measurements. The mean of serum vitamin D concentration in our cohort was 58.2 nmol/L at first visit. Phase II study found a 44% of a cohort of CD patients had serum vitamin D below 50

nmol/L. Our resulst are in agreement with other studies indicating vitamin D deficiency are more common among IBD patients than general population (Gaidos, Sultan, Dahl, & Valentine, 2011). Studies have shown a 62% of IBD patients had vitamin D deficiency and 88% of IBD patients (56 CD and 45 UC) had plasma vitamin D below 75 nmol/L (Alkhouri et al., 2013; Leslie et al., 2008a). Comparing active CD patients with those in clinical remission, active disease patients had lower serum vitamin D concentrations (Ham et al., 2014; Jørgensen et al., 2013).

It was hypothesized that providing vitamin D supplementation in doses higher than the RDA (> 600 IU/d) reduces the disease activity in Crohn's disease cases. The results of Phase 1 study are not conclusive. While the disease activity indicators were decreased in three cases, six cases had increased disease activity levels perhaps due to other factors such as surgery and disease complications. A study shows a daily vitamin D_3 supplement up to 400 IU did not significantly increase vitamin D status in participants with CD. Vitamin D_3 supplementation up to 2,000 IU/d for 6 months elevated plasma 25(OH)D above 30 ng/mL more effectively than 400 IU/d, but both achieved the cutoff of 20 ng/mL at 6 months (Wingate et al., 2014). A study shows a daily vitamin D_2 supplementation up to 2,000 IU for 6 weeks was insufficient to maintain the optimal levels in children and adolescents with IBD, while 2000 IU/day of vitamin D_3 and 50,000 IU/week were did (Pappa et al., 2014).

Boothe et al., (2011) found the doses of 10,000 IU had significant results in improving serum vitamin D when comparing 8 week (54.4±22.8) and after 26 week of treatment (64.2 ± 29.8) than 1000 IU/d. In our cohort, vitamin D levels improved significantly (p=.005) from baseline to the last visit (over 15 months) with decreasing the disease activity level hs-CRP significantly. A significant increase in vitamin D concentrations over 15 months was found in our CD cases who were receiving vitamin D supplement with mean intake of 1629 IU/d. In Phase I (case series), all our cases who were receiving 10,000 IU/d showed increased vitamin D

concentrations at week 9 (end of intervention) then declined at the follow-up. We observed different results from vitamin D supplementations and disease activity levels, and this limit us to draw an overall conclusion in Phase I study.

5.2 C- reactive protein, Disease activity index, and Health related quality of life

High sensitivity C-reactive protein was significantly associated with vitamin D levels among CD patients. Active Crohn's patients, based on endoscopy results, had high levels of hsCRP and vitamin D plasma below the optimal concentrations (< 75 nmol/L). All Phase I cases had hs-CRP levels above of 1 mgs/L at baseline. Only three cases showed decreased hsCRP levels after taking vitamin D supplement for 9 weeks. Phase II study have been shown vitamin D concentration was significantly associated with hsCRP level compared with deficient vitamin D category ($p < .05$). The disease activity indicator (hsCRP) decreased significantly over 15 months ($p=0.001$), while vitamin D concentration increased significantly ($p= 0.04$) in our cohort. In some cases in Phase I study, we found patients who were taking vitamin D supplement had increased vitamin D levels and improved their disease activity by decreasing hsCRP levels at 9 weeks. The hsCRP levels were increased in some cases perhaps because of other factors such as cancer and surgery. Use of corticosteroids had a positive association with hsCRP levels in our cohort ($p= 0.023$, Coef. 7.2). Steroids prescribed for short term to reduce the inflammation, however the risk factor for long term corticosteroid use including decrease calcium absorption and vitamin D metabolism are contribute to develop osteoporosis (Buckley, Leib, Cartularo, Vacek, & Cooper, 1996; De Sevaux, Hoitsma, Corstens, & Wetzels, 2002). In addition, all vitamin D categories (deficient as reference category) have shown a negative association with hsCRP levels. A study found oral vitamin D_3 supplementation up to 1200 IU/d for three months significantly increased vitamin D levels from a mean of 69 to 96 nmol/L and insignificantly decreased the disease

activity from 29% to 13% (p=0.06) (Jørgensen et al., 2010). Researchers show inactive CD patients who were treated with 0.25 μg alfacalcidiol ($1,25(OH)_2D_3$) for 6 weeks had significant reduction in disease activity plasma CRP concentrations of mean 15.8 ±23.57 mmol/L versus 7.81± 3.91 mmol/L (Miheller et al., 2009).

Harvey-Bradshaw Index and Crohn's Disease Activity Index were the only indicators to subjectively estimate the disease activity in our Phase I and HBI in Phase II study. In our cohort, the HBI scores show a significant association ($p<0.05$) with insufficient vitamin D levels only. Clinically, we found 18.2% of CD cases had active disease at baseline comparing to 32.6% were in remission according to HBI score. An inverse relationship was found from HBI and CDAI comparing to clinical biomarker (hsCRP). The CDAI did not correlate with ileocolonic inflammation; Crohn's patients who were in remission (defined by a CDAI score less than 150 points) had active disease (colonic inflammation) by endoscopy and vice versa (Modigliani et al., 1990). Only 38 patients out of 131 were in clinical and endoscopic remission (Modigliani et al., 1990). The heavily weighted symptoms in CDAI and HBI such as general well-being, abdominal pain and diarrhea were not considered as specific biomarkers of intestinal inflammation (Modigliani et al., 1990). In both studies, we found the results on hsCRP as the outcome variable were more interpretable than the subjective tools.

Disease duration and surgery did not reach statistical significance with hsCRP levels and HBI scores. A study indicated CRP levels during a relapse were not significantly associated with surgeries and duration of disease (Koelewijn, Schwartz, Samsom, & Oldenburg, 2008). However, the HBI score was positively associated with use of corticosteroids (p=0.000, OR= 5.5) and insufficient vitamin D category only (p=0.034, OR= 3.4) in our cohort. Using oral corticosteroids was more prevalent to patients who were vitamin D deficient (<25 nmol/L) comparing to normal levels group (> 50 nmol/L) (Chatu et al., 2013). In addition, use of corticosteroids drugs to

achieve remission for active disease were more effective than defined-formula diets (Messori et al., 1996).

Health-Related Quality of Life was used to quantify the degree of the impact of vitamin D supplementation in our cases. The HRQOL scores were improved in some cases after receiving supplementation for two months. Quality of life correlated with disease activity in CD, but it was influenced by other factors such as disease severity, corticosteroid use, smoking and surgery in the past three months (Blondel-Kucharski et al., 2001).

5.3 Dietary pattern, Healthy eating index, BMI and physical activity

In Phase I study, most of our cases had inadequate intake of vitamins including vitamins D, C and E. Important minerals including calcium, iron and zinc were below the RDA levels for healthy people. Moreover, all our cases had poor diet or needs improvement in their diet according to HEI. Poor dietary intakes cause malnutrition and micronutrients deficiencies especially those nutrients related to bone health and anemia, are more common in IBD (O'Sullivan & O'Morain, 2006). Vitamins and minerals deficiencies should be prevented by advising patients to consume food containing vitamins and minerals or supplements to avoid series of related health consequences (Goh & Morain, 2003; O'Sullivan & O'Morain, 2006). Enteral nutrition is recommended as a primary therapy for CD (when the small intestine is affected), which controls the inflammation and helps to reach remission (Lucendo, 2009).

BMI is affected by food intake and physical activity. In Phase I, we found only three cases were underweight and two were overweight according to BMI categories. Most patients (8 out of 9) had sedentary activity levels. As CD patients were at risk of malnutrition due to loss of appetite, medication side effects or malabsorption of nutrients (CCFC, 2001). In addition, intestinal inflammation interferes with food absorption, which leads to a weight classification of underweight BMI category (CCFC, 2001). A recent study found 40% of CD outpatients had

BMI $\geq$ 25 kg/m^2 and this was significantly associated with several factors including older age and lower level of physical activity (Nic Suibhne et al., 2013).

5.4 Socio-economic and demographics

In Phase I study, participants had different household income levels including upper-middle, lower- middle and lowest income levels. All our cases except one from Saskatoon were educated. Due to the small sample size, no statistical analysis could be performed to examine the socio-economic and demographics variables associated with CD. A study was done using the population-based University of Manitoba IBD Database, showed IBD cases were not higher socioeconomic status compared to general population (Bernstein et al., 2001).

6. Challenges and limitations

One limitation of Phase I study is a small sample size. Participant's recruitment was 9 months in Riyadh and one year in Saskatoon, and we recruited small number of participants. Most participants were not newly diagnosed and they had a history of surgery, which is one of our exclusion criteria. Some participants were living outside of the city and they were not able to come each visit, which lead to missing follow-up. Some patients did not adhere to the instructions to take vitamin D on a daily basis. In addition, some patients did not want to be blinded in the study and others resisting to be in the treatment groups with lowers doses. Another limitation is recall bias from the questionnaires that we provided (PAC and HRQOL). In addition, calprotectin measurement was not available at King Khaled University Hospital, and it was difficult to manage it in other laboratory outside the hospital. Laboratory tests were not done at the same time points of measurements. All these limitations affect our phase I results.

The main limitation in Phase II study was the retrospective nature of the data that limited us to only available information in patients' charts with relatively frequent missing data. We used GEE method to overcome the challenge with missing data considering that they were missing completely at random.

7. Recommendation for future research and practice

Vitamin D status of CD cases should be assessed regularly, and recommendation for vitamin D supplement intake should be provided accordingly. The role of vitamin D in autoimmune diseases and the possibility of higher requirements to vitamin D in CD patients warrant further researches with higher doses of vitamin D. Large randomized clinical trials are required to understand the impact of vitamin D supplements especially higher doses what is recommended to general population, such as 4000 IU and 10,000 IU/d, in CD patients in different ethnicities and environmental factors.

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Appendix 1

Table 2.11 Studies on Vitamin D and IBDs

Author, year	Study design	Participants	Data collection	Measure of Vit D	Dietary assessment for Vit D	Other measures	Key findings
Jørgensen, 2013	Cross-sectional study	182 CD patients and 62 healthy controls Median age 36 and 32 y Denmark	Jan 2000 - Dec 2008	Serum 25(OH) D	Vit D 400 IU/d or more (not >800 IU/d)	CDAI CRP	Active CD was associated with low serum 25-OH vitamin D. Patients who smoked had lower 25-OH vitamin D levels than patients who did not smoke.
Yang, 2013	Opened-labeled prospective clinical trial	18 CD patients age 18-70 US	-	Serum 25(OH) D_3	Vit D_3 1000 IU/d (2wk)-taking 5,000 IU/d to reached 40 ng/ml 25(OH)D3	CDAI IBDQ BMD 24-hour recalls, IL-10,IL-17 PTH Ca albumin ESR TNF-α	24 weeks supplementation with up to 5,000 IU/d vitamin D3 effectively raised serum 25(OH)D3 and reduced CDAI scores in a small cohort of CD suggesting that restoration of normal vitamin D serum levels may be useful in the management of patients with mild-moderate Crohn's disease.
Ashwin, 2012	Prospective cohort study	72,719 women (age 40–73 y) enrolled in the Nurses' Health Study US	1986- 05,2008	Serum 25(OH) D total Vit D intake (diet - supplements)	-	Hazard ratio (HR) for incident CD or UC	Higher predicted plasma levels of 25(OH) D significantly reduce the risk for incident CD and non-significantly reduce the risk for UC in women

Hassan, 2012	Cross sectional study	60 IBD patients (34 UC, 26 CD) Iran	-	Serum 25(OH) D	-	Disease activity (CDAI)	There is no association between Vit D deficiency and disease activity in relatively small number of IBD patients in a short period of time.
Nicholson, 2012	Systematic review	-	-		Vit D supplements	-	Vit D supplementation as an adjunctive treatment, may help in controlling colitis, this evidence is not enough to justify using vit D in treating IBD.
Papa, 2012	Clinical trial	61 IBD patients with 25(OH) D <20 ng/ml age 5-21 US	Nov 2007- June 2010	Serum 25(OH) D	Vit D2 supplements 2000IU/d, Vit D3 2000 IU/d, Vit D2 50,000 IU/wk	PTH	2,000 IU/d of vit D_3 and 50,000 IU vit D_2 weekly for 6 wk are superior to 2,000 IU vitamin D_2 daily for 6 wk in raising serum 25OHD concentration and are well-tolerated among children and adolescents with IBD. The change in serum PTH concentration did not differ among arms.
Boothe, 2011	Clinical trial	15 CD patients with 25(OH)Vit D <30 ng/ml US		Serum 25(OH) D	Vit D3 supplements (1000-10,000 IU/d)	HBI	Supplementation with 10,000 IU/d of Vit D3 may been effective adjunctive therapy for ameliorating symptoms in CD.
Kelly, 2011	Prospective	75 adults with quiescent CD Ireland	-	Serum 25(OH)D	-	Serum IL-10 TNF-alpha	Circulating levels of IL-10, but not TNF-alpha, were significantly lower in CD patients with inadequate serum 25(OH) D.
Hughes, 2011	Case–control	1359 Irish: - 660 adult (41.24 age)(M=291,F=369) CD(413),UC(247) - 699 healthy controls (40.15 age)(M=341,F=385) Ireland	-	VDR	-	IBD (Diagnose - location)	No significant association between any of the polymorphisms and risk of IBD for either heterozygotes or rare allele homozygotes. No significant differences in our results when analyzed by disease subtype (CD or UC) or by sex

Ulitsky, 2011	Cohort	504 IBD patients: 403 [CD] (age 43.3Y)(disease duration of 15.5 y) 101[UC] (age 42.4Y) (disease duration 10.9 y) US	'	Plasma 25(OH) D	-	(UCDI-HBI) HRQOL Vitamin B_{12}, folate, iron, albumin	Vit D deficiency is common in IBD and is Independently associated with lower HRQOL and greater disease activity in CD
Eloranta, 2011	Case–control	N=884 (M=404- F=480) 248 non-IBD controls - 636 IBD cases; 232 UC-404 CD - Age: 43.0 Switzerland	'	No measure	-	Colonoscopy diagnosis of UC or CD	DBP adds to the list of potential genes that contribute to the complex genetic etiology of IBD, and further emphasizes the association between vit D homeostasis and intestinal inflammation
Jorgensen, 2010	Clinical trial	108 CD patients in remission Denmark	One year	-	(n=46)1,200 IU VD_3+1,200 mg Ca n=48 placebo+1,200 mg Ca	CRP, haematocrit, Ca, albumin	Oral supplementation with 1,200 IE vit D3 significantly increased serum vit D levels and insignificantly reduced the risk of relapse from 29% to 13%, (p= 0.06)
Miheller, 2009	Prospective	37 inactive CD patients, A=17(f=7,m=10) age mean(32.94±10.96y) B=19(f=8,m=11) age mean(33.42±11.45y) Hungary	'	-	Group A= 1000 mg Ca Group B= 1000 IU VD_3	BMD Ca,PTH Iron,TP,cholesterol,triglyceride CRP,full blood count,ESR, OC,BCL	aVD has a more prominent short-term beneficial effect on bone metabolism and disease activity in CD compared with pVD.

Joseph, 2008	Case– control	34 Adult patients with CD above 18 yr. (m=24-f=10) age 39.2±12.9 Controls patients diagnosed IBS (m=24-f=10) age 38.9±13.4 India	08,2004- 04,2007	Serum 25(OH)D	-	Ca, Phosphorus, Alkaline phosphatase, 24h urinary ca, excretions of ca phosphate creatinine	Metabolic bone disease is a significant problem in patients with Crohn's disease. The main pathophysiological mechanisms involved include impaired absorption of calcium and vitamin D, treatment with steroids and the effect of the chronic inflammatory process on bone.
Pappa, 2006	cross-sectional	130 patients with IBD, ages 8 to 22y US	02, 2003 - 01,2005	Serum 25(OH)D	Vit D supplements	PTH Serum Ca LSBMD BMI	VitD deficiency is highly prevalent among pediatric patients with IBD. Factors predisposing to the problem include having a dark-skin complexion, winter season, lack of VitD supplementation, early stage of disease, more severe disease, and upper GI tract involvement in patients with CD.
Abreu, 2004	Review patients' medical records	138 patients with CD (M=75,F=63),mean age 37.7y 29 with UC (M=17,F=12) mean age 38.1y US	01,2002- 08,2002	Serum 25(OH)D 1,25(OH)$_2$D	-	Serum iPTH fractional urinary ca excretion LSBMD - nondominant proximal femur	-Elevated 1,25(OH)2D is more common in CD than previously appreciated and is independently associated with low bone mineral density -Normal 25(OH)D and elevated 1,25(OH)2D is in contrast with previous studies demonstrating low 25(OH)D and secondary hyperparathyroidism in patients with CD
Silvennoinen,1996	Case– control	IBD cases N=150 (M=79- F=71) age 40.0 Controls N=73 (M=35-F=38) age 40.8 Finland	-	Serum 25(OH)D	VD supplementation and dietary intake	serum Ca, P, iPTH Blood leukocytes	Patients with IBD have lower serum levels of 25(OH)D than healthy controls, but similar serum PTH concentrations and vitamin D intake. Vitamin D intake, and the serum levels of 25(OH)D and PTH are not associated with BMD, and malabsorption is unlikely to be a major factor in the aetiology of bone loss in unselected IBD patients.

Appendix 2

Table 3.4 Measured Biomarkers for Inflammation and Disease Activity

Biomarkers	Type of test	Range	Study sites	
			Saskatoon	Riyadh
hsCRP[1]	Blood test	Low risk: less than 1.0 mg/L Average risk: 1.0 to 3.0 mg/L High risk: above 3.0 mg/L	√	√
Albumin[1]	Blood sample	*Normal range:* 3.4 - 5.4 grams per deciliter (g/dL) (medlineplus, 2013).	√	√
WBC [2]	Blood sample	*Normal range:* 4,500 to 10,000 cells/mcL	√	√
Fecal calprotectin	Stool test	-Standard range (10-600 µg/g or 0.01-0.6 mg)) optimal range for differentiating IBD from IBS. -Extended range (30-1800 µg/g or 0.03-1.8 mg) advantageous in mentoring mucosal inflammation& disease activity.	in research only	-
CDAI	Tool	>150 indicates active disease < 150 indicates a remission	√	√ (in research only)
PCDAI	Tool	≤ 10 inactive disease 11-30 mild disease ≥ 30 moderate-to-severe disease	√ (in research only)	√ (in research only)

[1]*Routinely checked in study site(s)*

[2]*Note:*

- *cells/mcL = cells per microliter*

Note. Adopted from (ALPCO, 2014; Institute of Medicine, 2010; MedlinePlus, 2012, 2013)

UNIVERSITY OF SASKATCHEWAN

Appendix 3:PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE

The impact of Vitamin D on disease activity in Crohn's disease

PRINCIPAL INVESTIGATOR:
Hassanali Vatanparast, Associate Professor, College of Pharmacy and Nutrition, University of Saskatchewan

SUB-INVESTIGATORS:
Dr. Jennifer Jones, Assistant Professor of Medicine, University of Saskatchewan
Dr. Hani Jawa, Assistant Professor of Medicine, King Abdulaziz University
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STUDENT RESEARCHER:
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SPONSORS
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INTRODUCTION

You are invited to take part in this research study because you are recently diagnosed with Crohn's disease. There have been reports on the positive impact of vitamin D in controlling disease activity in autoimmune diseases such as Crohn's disease. The knowledge of the scientific community on the impact of vitamin D on Crohn's disease is very limited. Our research team designed this study as a MSc Thesis Project to evaluate the intake of high safe dose of vitamin D (10,000 IU/d) in disease activity. Mrs. Dania Alrefai will be conducting this study under direct supervision of Dr. Hassanali Vatanparast and members of the Advisory Committee.

It is up to you to decide whether or not you wish to take part. If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, you will not lose the benefit of any medical care to which you are entitled or are presently receiving. It will not affect your relationship with any of the investigators and researchers. Your family physician will be informed of your involvement in the study. Please take time to read the following information carefully. You can ask the researcher to explain any words or information that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family physician before you decide.

WHO IS CONDUCTING THE STUDY?

The study is being conducted by Mrs. Dania Alrefai, Dr. Hassanali Vatanparast, Dr.Jennifer Jones from the University of Saskatchewan, Dr. Hani Jawa from King Abdulaziz University and Dr. Wael El-matary from University of Manitoba. Along with in kind contributions from Royal University Hospital at the University of Saskatchewan, King Abdulaziz Hospital in Jeddah, Saudi Arabia, and Eruo-pharm Company, Saudi Arabian Cultural Bureau will partly cover the costs of this study. However, neither the institution nor any of the investigators or staff will receive any direct financial benefit from conducting this study.

WHY IS THIS STUDY BEING DONE?

This study is being done because only a few published studies measured Vitamin D levels in Crohn's disease patients in Saudi Arabia and Canada. The majority of studies on Crohn's disease and Vitamin D used regular dose of vitamin D supplementation. To our knowledge, there is only one unpublished study which has been conducted in the United States to determine the effect of high doses of Vitamin D (1000 and 10,000 IU/d) on Crohn's disease. As of yet, there has been no clinical trial in Saudi Arabia or Canada that explores the relationship between Crohn's disease and of Vitamin D supplements in safe doses higher than regular dose of 400 IU/d.

WHO CAN PARTICIPATE IN THE STUDY?

You are eligible to participate in this study if you are over 16 years of age and have been recently (≤2 years) diagnosed with an active Crohn's disease. Patients in remission or the duration of disease of more than 2 years, pregnancy, liver or kidney failure, and inability to take oral supplements or medicine will not be eligible to participate in this study.

Notice to women of child-bearing age:

- The effect of high doses of vitamin D on the fetus may be harmful.
- If you are pregnant or are a nursing mother you may not participate in this study.
- If you are able to have children and are sexually active you must agree to not become pregnant during the study and must agree to use acceptable methods of birth control until 30 days after the last dose of study drug. The study doctor will discuss these methods with you.
- If you believe you have become pregnant, you must inform your study doctor immediately and you will be withdrawn from the study. Your study doctor will continue to monitor the pregnancy to termination or delivery. The newborn infant will be monitored for at least 30 days after birth.

WHAT DOES THE STUDY INVOLVE?

This pilot study is a double-blind randomized control trial. After the initial screening on your disease activity and other indicators of health, you will be assigned to one of the study arms where you receive vitamin D in an assigned dose. Vitamin D supplements will be provided to you at two time points at the beginning of the study and at week four, when you return the empty bottle. Along with completing some questionnaires, your blood and fecal samples will be taken in three time points, at the beginning of the study, at week 9 (end of supplementation) and

week 15 (follow up). In addition to your regular visits with your physician, a study personnel will be in communication with you throughout the study to hear from you any concerns or changes in disease/health status related to Crohn's disease.

During the study period, you will take vitamin D supplements for 9 weeks. We will record available information related to your disease from your file. In addition to collecting some limited socio-demographic information, we will assess your dietary intake and physical activity using questionnaires. We will also measure your height and weight. Further, laboratory examinations to assess your disease status will include CBC, WCC, Vitamin D and Crohn's disease activity index. These laboratory tests will be conducted at the beginning of study, week 9 and after 2 months follow up.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

By enrolling in this study, you will receive free examination and advanced measurements on your disease status as well as free supplementation for a period of 9 weeks. Further, a full report on your health status will be provided to you through your family physician upon completion of our study. It is hoped the information gained from this study can be used to benefit patients with Crohn's disease.

ARE THERE POSSIBLE RISKS AND DISCOMFORTS?

If you choose to participate in this study, no known risks have been reported on Vitamin D intake of 10,000 IU/d according to the Food and Nutrition Board (FNB) at the Institute of Medicine where recommendations on nutrient intake is set. We will monitor your health status throughout the study to prevent any unlikely event. [1]

You may have early symptoms of hypercalcemia (high level of calcium in the blood) which can include:

- Weakness
- Fatigue
- Somnolence
- Headache
- Dry mouth
- Metallic taste
- Nausea
- Vomiting
- Vertigo
- Tinnitus
- Ataxia
- Hypotonia
- Anorexia

May have more serious manifestations which can include:

- Nephrocalcinosis
- Renal dysfunction
- Calcification
- Osteoporosis in adults
- Impaired growth in children
- Seizures

[1]Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

During the course of this study, new information that may affect your willingness to continue to participate will be provided to you by the researcher.

WHAT HAPPENS IF I DECIDE TO WITHDRAW?

Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. There will be no penalty or loss of benefits if you choose to withdraw. Your future medical care will not be affected. If you choose to enter the study and then decide to withdraw later, all data collected about you during your enrolment will be retained for analysis.

WILL I BE INFORMED OF THE RESULTS OF THE STUDY?

The results of the study will be available to participants on September 2014 from Dania Alrefai and Hassanali Vatanparast. The results will be presented in a Master's thesis, and may also be presented at conference presentations and published in journal articles. However, the results cannot be traced back to the individual participants. Following completion of the study, the research findings should be used as scientific evidence on the impact of Vitamin D on disease activity at Crohn's disease. This study will not contribute to any commercialization ventures.

WHAT WILL THE STUDY COST ME?

You will not be charged for any research-related procedures. You will not be paid for participating in this study. You will not receive any compensation, or financial benefits for being in this study, or as a result of data obtained from research conducted under this study.

WHAT HAPPENS IF SOMETHING GOES WRONG?

In the unlikely event of any adverse event related to the study occurs, you should seek immediate care and, as soon as possible, by notifying us through the contact information in consent form. Necessary medical treatment will be made available at no cost for you. By signing this document, you do not waive any of your legal rights should you need to seek compensation for damages which arise.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected.

The study data will be stored securely (in a locked cabinet contained within a locked office under the supervision of the PI) by the study team for a length of time for a maximum of five years post publication. Your name will not be attached to any information, nor mentioned in any study report, nor be made available to anyone except /for the research team. Confidentiality will be attained by use of a unique numeric identification number. Your data with be combined with data from other participants in aggregated form so that no individual identity is disclosed. However, research records and medical records identifying you may be inspected in the presence of the

Investigator and/or the University of Saskatchewan Research Ethics Board for the purpose of monitoring and verifying the integrity of the research data. Scientific presentations or publications will not disclose individual identity.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

If you have any questions or desire further information about this study before or during participation, you can contact Dr. Hassan Vatanparast at 306-966-6341. If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-966-2975 (out of town calls 1-888-966-2975). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.

In case of emergency you can call Dr. Hassan Vatanparast at …… any time.

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CONSENT TO PARTICIPATE

Study Title: The impact of vitamin D on disease activity in Crohn's disease

- I have read (or someone has read to me) the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I understand that I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future relationships.
- I give permission to the use and disclosure of my de-identified information collected for the research purposes described in this form.
- I understand that by signing this document I do not waive any of my legal rights.
- I will be given a signed copy of this consent form.

I agree to participate in this study:

_____
Printed Name of Adult Study Participant

_____
Signature of Adult Study Participant Date

_____
Printed Name of Person Explaining Consent Form

_____
8.1 Signature of Person Explaining Consent Form
Date

UNIVERSITY OF SASKATCHEWAN

CONSENT FORM **نموذج إقرار**

The impact of vitamin D on disease activity in Crohn's disease.

Principal Investigator:
Dr. Abdelrahman Aljebreen

Co-Investigator(s):
Dr. Othman Alharbi
Dr. Majid Almadi
Dr. Nahla Azzam

Student:
Dania Alrefai

الباحث الرئيس:
د. عبدالرحمن الجبرين

الباحث المشارك:
د. عثمان الحربي
د. ماجد الماضي
د نهلة عزام

الطالبه: دانيا الرفاعي

You are being asked to participate voluntarily in a Research Study. If you decide to take part in this study, please sign this consent form and return it.

نرجو منك المشاركة في هذه الدراسة البحثية وعند موافقتك بذلك ترجو منك التوقيع على هذه الورقة وإرجاعها إلينا

STUDY PURPOSE: To study the impact of vitamin D on disease activity in Crohn's disease in Saudi Arabian patients.

الهدف من الدراسة:
تحديد أثر مكملات فيتامين د على نشاط المرض في المرضى الذين يعانون من داء كرون في المملكة العربية السعودية.

STUDY PLAN:
This pilot study is a double-blind randomized control trial. The duration of study is 9 weeks and 2 months follow up later.
If you decide to Participate in this study.

- You will be assigned to one of the study arms (400IU, 2000IU, 10,000IU Vitamin D) where you receive vitamin D in an assigned dose and you will not know which group you will be assign.
- Vitamin D supplements will be provided to you at two time points at the beginning of the study and at week five, when you return the empty bottle.
- Along with filling out some questionnaires e.x socio-demographic, physical activity and health related quality of life, your blood and fecal samples would be taken in three time points, at the beginning of the study, at week 9 and week 15.

خطه البحث:

هذه الدراسه تجربه عشوائيه لمده ٩ اسابيع و شهرين اخرين للمتابعه.
في حال قبولك للمشاركة:

- سوف تسجل في واحده من المجموعات التي سوف تأخذ مكملات فيتامين د (٤٠٠ وحده دوليه، ٢٠٠٠ وحده دوليه او ١٠،٠٠٠ وحده دوليه) دون علم اي مجموعه سوف تكون
- سوف نقوم بإعطائك مكملات فيتامين د مرتين (في بدايه الدراسه و في الآسبوع الخامس عند ارجاع العلبه الآولى).
- سوف تقوم بتعبئه بعض الإستبيانات عن الحاله

UNIVERSITY OF SASKATCHEWAN

- In addition to regular visits that you have with your physician, a study personal will be on communication with you thought the study to hear from you any concerns or changes in disease/health status relate to Crohn's disease.

الاجتماعيه و النشاط الرياضي و الحاله الصحيه.
اخد عينه من الدم ٣ مرات خلال مده الدراسه (في الآسبوع الأول، الآسبوع التاسع، و نهايه الدراسه)

- سوف يقوم الباحث بالتواصل معك و اخباره في حاله وجود اي تغييرات صحيه مصاحبه للمرض

BENEFITS: The result of this study may not benefit you directly, but in the future with God's will the patients will benefit from the knowledge acquired.

الاستفادة المرجوة من الدراسة: إن الاستفادة من هذه الدراسة قد لا تعود عليك مباشرة ولكن قد تكون لنتائج هذا البحث تأثيرات على معالجة المرضى الآخرين.

SIDE EFFECT: If you choose to participate in this study, no known risks or side effect have been reported on Vitamin D intake of 10,000 IU/d according to the Food and Nutrition Board (FNB) at the Institute of Medicine where recommendations on nutrient intake is set

الآثار الجانبية: اذا اردت المشاركه في البحث، ليس هناك اي خطر او اعراض جانبيه للجرعات المقدمه في هذه الدراسه وفقا لتوصيات منظمه الغذاء و التغذيه في معهد الطب.

REFUSAL: If you refuse to participate, there will be no penalty or loss of benefits. You can leave the study at any stage without any negative consequences to the level of care you will receive

عدم الرغبة في المشاركة: إذا رفضت المشاركة في هذه الدراسة فإنك لن تتعرض لأي جزاء أو فقدان للمزايا العلاجية. تستطيع ان تغادر الدراسه في اي وقت بدون اي عواقب.

CONFIDENTALITY: Your participation in this study will be kept confidential. The results of this research may be published, however, your identity will never be revealed.

سرية المعلومات: إن شاركتك في هذه الدراسة ستكون في غاية السرية. قد يتم نشر النتائج هذا البحث لأغراض أكاديمية ولكن لن يتم الكشف عن هويتك في أي حال من الأحوال.

APPROVAL: I fully understand the information and the consent form.

الموافقة بالمشاركة: استوعبت المعلومات في هذا النموذج, لذا أوافق بالمشاركة في هذه الدراسة. كما أنني لا أمانع من استخدام العينات المتحصل عليها من هذه الدراسة بأن تستخدم في دراسات مستقبلية من قبل الباحثين.
لقد تم شرح هذا النموذج للمتبرع بواسطة أحد الباحثين قبل طلب التوقيع منه.

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I sign freely and voluntarily. A copy has been given to me.

أوقع أنا بمحض إرادتي وحريتي وقد تم إعطائي نسخة من الإقرار.

Investigator or Associate:

أسم الباحث أو من ينوب عنه:

Signature:
Date:

التوقيع:
التاريخ:

Patient Name:

أسم المريض:

Signature:
Date:

التوقيع:
التاريخ:

Witness Name:

أسم الشاهد:

Signature:
Date:

التوقيع:
التاريخ:

If you have any further concerns or questions, you can contact Dr. Majid Almadi (Bleep # 000. Ext. # 000)

عند الرغبة في أي استفسار عن هذه الدراسة يمكنك ألاتصال بالدكتور ماجد الماضي على تليفون رقم 000. تحويلة 000.

The impact of Vitamin D on disease activity in Crohn's disease

Baseline Visit 1

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ ___ — ___ ___ ___ ___ ___ ___

Site # Screening # Initials

Appendix 4: Baseline form

SOCIO-DEMOGRAPHICS

First Name: Last name:
Home address: Phone number:

Date of Birth: __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Age: _____

Sex: Male ☐ Female ☐

Household type (ie. mother only, father only, both parents):

Total number of individuals in the household:
Number of children in household:

Socio-demographic characteristics (SDC)

1. **I**ndicate your migration status:
   - ☐ Immigrant (permanent resident)
   - ☐ Refugee (permanent resident)
   - ☐ Canadian Citizen
   - ☐ Student or worker (temporary resident)
   - ☐ Non status (unrecognized immigrant)

2. In what country you born?

3. What date did you (participant) first come to (Canada/ Saudi Arabia) (MM/DD/YY) (must be < 5 years)? If the participant was born in Canada, indicate when family arrived.
_____

4. People living in (Canada/ Saudi Arabia) come from many different cultural and racial backgrounds. Are you:

- ☐ White
- ☐ Chinese
- ☐ South Asian (e.g., East Indian, Pakistani, Sri Lankan)
- ☐ Black
- ☐ Latin
- ☐ American
- ☐ Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese, Burmese)
- ☐ Filipino
- ☐ Arab
- ☐ West Asian (e.g., Afghan, Iranian)
- ☐ Japanese
- ☐ Korean

5. What languages do you speak (list all, including English)?

6. What language do you speak most often at home?

7. What is the language that you first learned at home?
8. Can you still…?
- ☐ Speak and understand your first language
- ☐ Only understand your first language
- ☐ Neither speak nor understand your first language

Education (EDU)

9. What is your (participant's) highest grade of elementary school completed in your home country?

10. Father's education in home country:
- ☐ <Grade 8
- ☐ <Grade 12
- ☐ High school diploma
- ☐ Some University
- ☐ University degree-Indicate highest degree_____
- ☐ Trade/other education-Indicate certification_____
- ☐ Refuse to answer

11. Father's education in (Canada/ Saudi Arabia):
- ☐ High school diploma
- ☐ Some University
- ☐ University degree-Indicate highest degree_____
- ☐ Trade/other education-Indicate certification_____
- ☐ Refuse to answer

12. Mother's education in home country:
- ☐ <Grade 8
- ☐ <Grade 12
- ☐ High school diploma
- ☐ Some University
- ☐ University degree-Indicate highest degree_____

- ☐ Trade/other education-Indicate certification_____
- ☐ Refuse to answer

13. Mother's education in (Canada/ Saudi Arabia):

- ☐ High school diploma
- ☐ Some University
- ☐ University degree-Indicate highest degree_____
- ☐ Trade/other education-Indicate certification_____
- ☐ Refuse to answer

Income (INC)

Although many health expenses are covered by health insurance, there is still a relationship between health and income. Please be assured that, like all other information you have provided, these answers will be kept strictly confidential.

14. What is your best estimate of the total income, before taxes and deductions, of all household members from all sources in the past 12 months? If participant has been in (Canada/ Saudi Arabia) less than 12 months, indicate average per month and multiply by 12. _____

- ☐ Refuse to answer

15. Thinking about the total income for all household members, from which of the following sources did your household receive any income in the past 12 months? If participant has been in (Canada/ Saudi Arabia) less than 12 months, indicate sources of income since arrival in (Canada/ Saudi Arabia).

- ☐ Wages and salaries
- ☐ Income from self-employment
- ☐ Dividends and interest (e.g. bonds, savings)
- ☐ Worker's compensation
- ☐ Retirement pensions, superannuation and annuities
- ☐ Old age security and guaranteed income supplement
- ☐ Provincial or municipal social assistance or welfare
- ☐ Child tax benefit
- ☐ Child support
- ☐ Alimony, other (e.g., rental income, scholarship)
- ☐ Refuse to answer

16. What was the main source of income?

- ☐ Wages and salaries
- ☐ Income from self-employment

- ☐ Dividends and interest (e.g. bonds, savings)
- ☐ Worker's compensation
- ☐ Retirement pensions, superannuation and annuities
- ☐ Old age security and guaranteed income supplement
- ☐ Provincial or municipal social assistance or welfare
- ☐ Child tax benefit
- ☐ Child support
- ☐ Alimony, other (e.g., rental income, scholarships)
- ☐ Refuse to answer

17. Can you estimate in which of the following groups your household income falls? Was the total household income from all sources:

- ☐ less than $5,000
- ☐ $5,000 to less than $10,000
- ☐ $10,000 to less than $15,000
- ☐ $15,000 to less than $20,000
- ☐ $20,000 to less than $25,000
- ☐ $25,000 to less than $30,000
- ☐ $30,000 to less than $40,000
- ☐ $40,000 to less than $50,000
- ☐ $50,000 to less than $60,000
- ☐ $60,000 to less than $80,000
- ☐ $80,000 to less than $100,000
- ☐ $100,000 or more

The impact of Vitamin D on disease activity in Crohn's disease

Subject ID: ___ — ___ ___

Site # Screening # Initials

Baseline Visit 1

__ __/ __ __/ __ __ __ __

(dd/mm/yyyy)

DISEASE RELATED INFORMATION

1) Past History

Diagnosis: CD ☐ UC ☐ IC (Indeterminent colitis) ☐

Date of initial diagnosis __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Date of onset of symptoms __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Date of initial colonoscopy __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

IBD Phenotype

Disease Location for Crohn's Disease (check all that apply)

Grey boxes- minimum location to define extent. Non-shaded- prospective data or not in chart

	At Diagnosis	*At Enrollment* Date (dd/mm/yyyy)
Upper GI	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Small Bowel	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Jejunum	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Terminal Ileum	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Ileocecal Valve	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Colon	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Cecum	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Ascending	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown

Transverse	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Descending	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Sigmoid	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown
Rectum	☐ Bowel+, inflam + ☐ Bowel+, inflam - ☐ Bowel- or unknown	☐ Bowel+, inflam +: ☐ Bowel+, inflam - : ☐ Bowel- or unknown

Confirmation of Disease Location (check all that apply**):**

(dd/mm/yyyy)

☐ clinical chart note: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ endoscopy: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ radiology: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ operative: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ histopathology: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ other (comment box): Date of Confirmation __ __/ __ __/ __ __ __ __

Disease Behavior for Crohn's Disease (check all that apply)

Grey boxes- minimum data to define behavior. Non-shaded- prospective data or not in chart

	At Diagnosis Date (dd/mm/yyyy)	At Enrollment Date (dd/mm/yyyy)
Inflammatory	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
[a]**Fibrostenosis**	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Penetrating	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
[b] Internal fistula (not perianal)	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Abd. inflammatory mass	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Abdominal abscess	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown

Other		

[a]If fibrostenosis is checked, (check all that apply): ileal, colonic, other (comment)

[b] If Internal fistula is checked, then(check all that apply): entero-enteric, entero-cutaneous, peri-stomal fistula, entero-vesical, entero-vaginal, other (comment box)

If yes to entero-enteric
☐ ileal-ileal
☐ ileo-colonic
☐ gastro-colic
☐ colo-colic

If yes to enterocutaneous,
☐ enterocutaneous confirmed
☐ peristomal

Confirmation of Disease Behavior (check all that apply**):**

(dd/mm/yyyy)
☐ clinical chart note: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ endoscopy: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ radiology: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ operative: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ histopathology: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ other (comment box): Date of Confirmation __ __/ __ __/ __ __ __ __

Perianal Disease for Crohn's Disease (check all that apply)
Grey boxes- minimum data to define behavior. Non-shaded- prospective data or not in chart

	At Diagnosis Date (dd/mm/yyyy)	At Enrollment Date (dd/mm/yyyy)
Perianal Fistula	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown

Perianal Abscess	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Anal ulceration	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Anal stenosis	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown

Confirmation of Perianal Disease (check all that apply**):**

(dd/mm/yyyy)

☐ clinical chart note: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ endoscopy: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ radiology: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ operative: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ histopathology: Date of Confirmation __ __/ __ __/ __ __ __ __
☐ other (comment box): Date of Confirmation __ __/ __ __/ __ __ __ __

Evidence of granuloma on histopathology at any time

☐ Yes ☐ No ☐ Unknown
If YES then: __ __/ __ __/ __ __ __ __ dd/mm/yyyy

Hospitalization for IBD Flares:

☐ Yes ☐ No ☐ Unknown
If YES then:

Number of Hospital Admissions: ☐ 1
☐ 2
☐ > 2
☐ unknown

Date of First Hospital Admission: __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

The impact of Vitamin D on disease activity in Crohn's disease

Baseline Visit 1

__ __/ __ __/ __ __ __

(dd/mm/yyyy)

Subject ID: | | | — | | | | | | |

Site # Screening # Initials

Crohn's Disease Past Medication

Medication	Dose	Route	Frequency	Start Date	End Date
5-ASA					
6MP					
Azathioprine					
Prednisone					
Budesonide					
Methotrexate					
Cyclosporine					
Infliximab					
Adalimumab					

List of:

Supplements
1. _____
2. _____
3. _____

Probiotics
1. _____
2. _____
3. _____

Herbal
1. _____
2. _____
3. _____

The impact of Vitamin D on disease activity in Crohn's disease

Subject ID: ___ — ___ ___

Site # Screening # Initials

Baseline Visit 1

__/__/____

(dd/mm/yyyy)

Surgical History

Appendectomy Yes ☐ No ☐ Others _____	
Has a resection been performed?	Yes ☐ No ☐
If yes, please record Crohn's disease surgical history below.	
Site of Resection:	
1.	Date:
2.	Date:
3.	Date:
4.	Date:

Crohn's Disease Medication Presently

Medication	Dose	Route	Frequency	Start Date	End Date
5-ASA					
6MP					
Azathioprine					
Prednisone					
Budesonide					
Methotrexate					
Cyclosporine					
Infliximab					
Adalimumab					

The impact of Vitamin D on disease activity in Crohn's disease

Baseline Visit 1
__ __/ __ __/ __ __ __
(dd/mm/yyyy)

Subject ID: | | | — | | | | | | |
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Extra-Intestinal Manifestations:

Joint: Arthralgia Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Arthirits Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Eyes: Uveitis Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Episcleritis Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Skin: Erythema Nodosum Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Pyoderma Gangrenosum Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Mucocutaneous: Oral Apthous ulcers Yes ☐ No ☐ Date __ __/ __ __/ __ __ __ __

Family History IBD-Associated Conditions:

PSC:

Parent Yes ☐ No ☐
Sibling Yes ☐ No ☐
Children Yes ☐ No ☐
Second degree Yes ☐ No ☐

Psoriatic Arthritis:

Parent Yes ☐ No ☐
Sibling Yes ☐ No ☐
Children Yes ☐ No ☐
Second degree Yes ☐ No ☐

Asthma:

Parent Yes ☐ No ☐
Sibling Yes ☐ No ☐
Children Yes ☐ No ☐
Second degree Yes ☐ No ☐

Eczema:

Parent Yes ☐ No ☐
Sibling Yes ☐ No ☐

Baseline Visit 1

__ __/ __ __/ __ __ __

(dd/mm/yyyy)

Subject ID: | | | — | | | | | | | |

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Children Yes ☐ No ☐
Second degree Yes ☐ No ☐

Colon Cancer:
Parents Yes ☐ No ☐
Sibling Yes ☐ No ☐
Children Yes ☐ No ☐
Second degree Yes ☐ No ☐

aternal smoking during pregnancy: Yes ☐ No ☐ Don't know ☐

ANTHROPOMETRICS EXAMINATION

Date of Assessment: __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

High _____ cm Weight _____ kg BMI _____ Blood Pressure _____ ☐ Not done

Waist circumference:

PHYSICAL ACTIVITY

1. Have you done any of the following in the past 3 months, that is, date three months ago) to yesterday?

☐ Walking for exercise
☐ Gardening or yard work
☐ Swimming
☐ Bicycling
☐ Popular or social dance
☐ Home exercises
☐ Ice hockey
☐ Ice skating
☐ In-line skating or rollerblading
☐ Jogging or running
☐ Golfing
☐ Exercise class or aerobics
☐ Downhill skiing or snowboarding
☐ Bowling
☐ Baseball or softball

- ☐ Tennis
- ☐ Weigh-training
- ☐ Fishing
- ☐ Volleyball
- ☐ Basketball
- ☐ Soccer
- ☐ Any other_____
- ☐ No physical activity

2. In the past 3 months, did you do any other physical activity for leisure?

- ☐ Yes_____
- ☐ No

3. In the past 3 months, how many times did you participate in identified activity?

4. About how much time did you spend on each occasion?

- ☐ 1 to 15 minutes
- ☐ 16 to 30 minutes
- ☐ 31 to 60 minutes
- ☐ More than one hour

Next, some questions about the amount of time spent in the past 3 months on physical activity at work, while doing daily chores around the hours, or doing errands, but <u>not</u> leisure time activity.

5. In a typical week in the past 3 months, how many hours did you usually spend walking to work or to school or while doing errands?

- ☐ None
- ☐ Less than 1 hour
- ☐ From 1 to 5 hours
- ☐ From 6 to 10 hours
- ☐ From 11 to 20 hours
- ☐ More than 20 hours

6. In a typical week in the past 3 months, how many hours did you usually spend bicycing to work or to school or while doing errands?

- ☐ None
- ☐ Less than 1 hour
- ☐ From 1 to 5 hours
- ☐ From 6 to 10 hours
- ☐ From 11 to 20 hours
- ☐ More than 20 hours

7. Thinking back over the past 3 months, which of the following best describes your usual daily activities or work habits?

☐ Usually sit during the day and don't walk around very much
☐ Stand or walk quite a lot during the day but don't have to carry or lift things very often
☐ Usually lift or carry light leads, or have to climb stairs or hills often
☐ Do heavy work or carry very heavy loads

Sun Exposure (SEB)

The next two questions are about your exposure to the sun since you have been in Canada. For these questions, think about a typical weekend or day off from school in the summer months.

1. About how much time each day do you spend in the sun between 11 am and 4 pm?

☐ None
☐ Less than 30 minutes
☐ 30 to 59 minutes
☐ 1 hour to less than 2 hours
☐ 2 hours to less than 3 hours
☐ 3 hours to less than 4 hours
☐ 4 hours to less than 5 hours
☐ 5 hours

2. In the summer months, on a typical weekend or day off from school, when you are in the sun for 30 minutes or more, how often do you use sunscreen?

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

Vitamin D:

1. Are you taking Vitamin D supplements on a **<u>regular daily</u>** basis?

☐ Yes
☐ No

If yes, please indicate the amount?

☐ 600 IU/d
☐ 1000 IU/d
☐ 2000 IU/d
☐ Other……

The impact of Vitamin D on disease activity in Crohn's disease

Subject ID: ___ ___ — ___ ___ ___ ___ ___ ___

Site # Screening # Initials

Baseline Visit 1

__ __/ __ __/ __ __ __ __

(dd/mm/yyyy)

LABORATORY TESTS – Screening Visit

__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Test	Concentration (units)
WBC	
Hg	
Hct	
Platelets	
Ferritin	
Vitamin D	
Serological Biomarkers	
hsCRP	
Fecal Biomarkers	
Calprotectin	

Safety measurments

__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Tests	Concentration (units)
Calcium	
Phosphate	
25(OH)D	
ALT, AST, BUN levels	
Magnesium	
Pregnancy test	

Creatinine	
GFR	
Urinalysis for hematuria	
PTH	
Albumin	

MEASURES OF DISEASE ACTIVITY

Harvey-Bradshaw Index for Crohn's Disease

A. General Wellbeing
0=Very Well
1=Slightly below par
2=Poor
3=Very poor
4=Terrible

B. Abdominal Pain
0=None
1=Mild
2=Moderate
3=Severe

C. # Liquid Stools/Day

D. Abdominal Mass
0=None
1=Dubious
2=Definite
3=Definite and tenderness

E. Complications
1=Arthralgia
1=Erythema Nodosum
1=Aphthous Ulcers
1=Pyoderma Gangrenosum
1=Anal Fissure
1=New Fistula
1=Abscess

Total Score= _____

The impact of Vitamin D on disease activity in Crohn's disease

Subject ID: ___ — ___ ___

Site # Screening # Initials

Baseline Visit 1

__ __/ __ __/ __ __ __

(dd/mm/yyyy)

2 CROHN'S DISEASE ACTIVITY INDEX

	SUBTOTAL
♦ **Number of liquid or very soft stools** Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X2 =	
♦ **Abdominal pain** (0=none; 1=mild, 2=moderate, 3=severe) Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X5 =	
♦ **General well-being** (0=generally well; 1-slightly under par; 2=poor; 3-very poor; 4-terrible) Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X7 =	

♦ **Number of 6 listed categories patient now has** (tick all that apply)

☐ Arthritis/Arthralgia ☐ Iritis/Uveitis ☐ Anal Fissure, Fistula or Abscess

☐ Other fistula ☐ Fever > 37.8° C during previous week

☐ Erythema Nodosum, Pyoderma Gangrenosum/Aphthous Stomatitis

Total X20 = **Total number of categories**

♦ **Taking Lomotil/opiates for diarrhea** (tick appropriate and report total)

☐ **Yes (30)** ☐ **No (0)**

♦ **Abdominal Mass** (tick appropriate and report total)

☐ **None (0)** ☐ **Questionable (20)** ☐ **Definite (50)**

♦ **Hematocrit** (Please enter hematocrit value and calculate)

Male **(47 –** (minus) ___ **%) x 6** =

Female **(42 –** (minus) ___ **%) x 6** =

♦ **Body weight**

= Body weight / Standard weight (1 - ___ kg / ___ kg) X 100

Tick appropriate box
Please add (underweight) +
Or subtract (overweight) –

♦ **(Please add all subtotals) CDAI TOTAL** ____

RISK FACTORS

Smoking Status:

- Ever smoked regularly, at least 1 cigarette/day for 3 or more months? Yes ☐ No ☐

- Currently smoke at least 1 cigarette / day Yes ☐ No ☐

- Current extent of smoking:
  - -1 to 5 cigarettes / month ☐
  - -1 to 5 cigarettes / week ☐
  - < 1/2 pack (10 cigarettes) / day ☐
  - 1/2 to 1 pack (20 cigs) / day ☐
  - > 1 pack / day ☐

How many years have you smoked at least 1 cigarette / day? -
_____

Do you currently reside with anyone who smokes inside the home? Yes ☐ No ☐

Regular Medications:

List all medications that you take on a regular basis:

Supplements
1. _____
2. _____
3. _____

Probiotics
1. _____
2. _____
3. _____

Herbal
1. _____
2. _____
3. _____

NSAID Use: Never ☐

Previously regular ☐

Current regular ☐

Have you been on antibiotics for 3 or more times in the past year?

Yes ☐ No ☐ Don't know ☐

Infections:

Ever diagnosed with Chicken pox? Yes ☐ No ☐ Don't know ☐

Ever diagnosed with measles? Yes ☐ No ☐ Don't know ☐

Ever diagnosed with shingles? Yes ☐ No ☐ Don't know ☐

Ever diagnosed with food poisoning? Yes ☐ No ☐ Don't know ☐

Ever diagnosed with gastroenteritis? Yes ☐ No ☐ Don't know ☐

Ever diagnosed with recurrent ear infections? Yes ☐ No ☐ Don't know ☐

Immunizations:

Received all childhood pneumococcal immunizations? Yes ☐ No ☐ Don't know ☐

Received all childhood meningicoccal immunizations? Yes ☐ No ☐ Don't know ☐

Received all childhood varicella immunizations? Yes ☐ No ☐ Don't know ☐

Received all childhood Hepatitis B immunizations? Yes ☐ No ☐ Don't know ☐

Received all Hepatitis A immunizations? Yes ☐ No ☐ Don't know ☐

Received teenage pertussis booster (teenager)? Yes ☐ No ☐ Don't know ☐

Received all HPV immunizations? Yes ☐ No ☐ Don't know ☐

Neonatal Breastfeeding:

Were you breastfed as a baby exclusively or nearly exclusively for longer than 4 months?

Yes ☐ No ☐ Don't know ☐

Family History:

First-degree relative with Ulcerative Colitis:

Mother ☐ Father ☐ Brother ☐ Sister ☐ Son ☐ Daughter ☐

First-degree relative with Crohn's Disease:

Mother ☐ Father ☐ Brother ☐ Sister ☐ Son ☐ Daughter ☐

Farm Exposure:

Have you ever lived on a farm?

During what years (i.e., 1990 to 1995) did you reside on a farm?

_____

What type of farm did you reside on?

☐-Dairy cattle
☐-Beef cattle
☐-Pigs
☐-Chicken/poultry
☐-Grain/wheat only
☐-Other _____

Well Water:

Has your main source of water ever been well water? Yes ☐ No ☐

During what years (i.e. 1990 to 1995) was well water your main source of water?

Unpasteurized Milk:

Have you ever routinely drunk unpasteurized milk? Yes ☐ No ☐

During what years (i.e. 1990 to 1995) did you routinely drink unpasteurized milk?

_____

The impact of Vitamin D on disease activity in Crohn's disease

Baseline Visit 1

__ __/ __ __/ __ __ __

(dd/mm/yyyy)

Subject ID: ___ — ___ ___

Site # Screening # Initials

Household Exposures:

How many people lived with you (including yourself)?

At age ☐ ☐ ☐6 ☐15 ☐ 30

How many bathrooms did you have in your home?

At age ☐ ☐ ☐6 ☐15 ☐30

Which pets did you have in your home?

- ☐ Cat
- ☐ Dog
- ☐ Bird
- ☐ Turtle
- ☐ Rabbit
- ☐ None
- ☐ Other _____

At age ☐ ☐ ☐6 ☐25 ☐ 30 ☐urrent

Single Child: Yes ☐ No ☐

First Born: Yes ☐ No ☐

DIETARY ASSESSMENT

First 24- dietary Hour Recall

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				

Evening Meal				
Before Bed				

Was this intake usual? Circle one:

- ☐ Yes
- ☐ No

If No, explain why not_____

Any vitamin / mineral intake during this time?

- ☐ Yes
  if Yes, list names:
- ☐ No

Second 24- dietary Hour Recall

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				
Evening Meal				

Before Bed				

Was this intake usual? Circle one:

☐ Yes
☐ No

If No, explain why not_____

Any vitamin / mineral intake during this time?

☐ Yes
if Yes, list names:

☐ No

Third 24- dietary Hour Recall

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				
Evening Meal				

Before Bed				

Was this intake usual? Circle one:

- ☐ Yes
- ☐ No

If No, explain why not_____

Any vitamin / mineral intake during this time?

- ☐ Yes
  if Yes, list names:

HEALTH RELATED QUALITY OF LIFE (IBDQ)

1. How frequent have your bowel movements been during the last two weeks?

- ☐ Bowel movements as or more frequent than they have ever been
- ☐ Extremely frequent
- ☐ Very frequent
- ☐ Moderate increase in frequency of bowel movements
- ☐ Some increase in frequency of bowel movements
- ☐ Slight increase in frequency of bowel movements
- ☐ Normal, no increase in frequency of bowel movements

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

5. How much of the time during the last 2 weeks have your bowel movements been loose?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time

- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

6. How much energy have you had during the last 2 weeks?

- ☐ No energy at all
- ☐ Very little energy
- ☐ A little energy
- ☐ Some energy
- ☐ A moderate amount of energy
- ☐ A lot of energy
- ☐ Full of energy

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

10. How often during the last 2 weeks have you felt generally unwell?

- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time

- ☐ None of the time

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? please choose an option from
- ☐ A great deal of difficulty; activities made impossible
- ☐ A lot of difficulty
- ☐ A fair bit of difficulty
- ☐ Some difficulty
- ☐ A little difficulty
- ☐ Hardly any difficulty
- ☐ No difficulty; the bowel problems did not limit sports or leisure activities

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

15. How often during the last 2 weeks have you felt depressed or discouraged?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas?

- ☐ A major problem
- ☐ A big problem
- ☐ A significant problem
- ☐ Some trouble
- ☐ A little trouble
- ☐ Hardly any trouble
- ☐ No trouble

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at.

- ☐ A major problem
- ☐ A big problem
- ☐ A significant problem
- ☐ Some trouble
- ☐ A little trouble
- ☐ Hardly any trouble
- ☐ No trouble

19. Many patients with bowel problems often have worries and anxieties related to their illness. these include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. in general, how often during the last 2 weeks have you felt worried or anxious?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time

- ☐ Hardly any of the time
- ☐ None of the time

21. How often during the last 2 weeks have you felt relaxed and free of tension?

- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ A good bit of the time
- ☐ Most of the time
- ☐ Almost all of the time
- ☐ All of the time

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

25. How much of the time during the last 2 weeks have you felt tearful or upset?

- ☐ All of the time
- ☐ Most of the time

- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

28.To what extent has your bowel problem limited sexual activity during the last 2 weeks?

- ☐ 1 no sex as a result of bowel disease
- ☐ 2 major limitation as a result of bowel disease
- ☐ 3 moderate limitation as a result of bowel disease
- ☐ 4 some limitation as a result of bowel disease
- ☐ 5 a little limitation as a result of bowel disease
- ☐ 6 hardly any limitation as a result of bowel disease
- ☐ 7 no limitation as a result of bowel disease

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

30. How much of the time during the last 2 weeks have you felt irritable?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

31. How often during the past 2 weeks have you felt a lack of understanding from others?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks?

- ☐ Very dissatisfied, unhappy most of the time
- ☐ Generally dissatisfied, unhappy
- ☐ Somewhat dissatisfied, unhappy
- ☐ Generally satisfied, pleased
- ☐ Satisfied most of the time, happy
- ☐ Very satisfied most of the time, happy

The impact of Vitamin D on disease activity in Crohn's disease

Week 5 Visit 2
__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ ___ — ___ ___ ___ ___ ___ ___

Site # Screening # Initials

Appendix 5: Week 5 form

First Name: Last name:
Home address: Phone number:

Date of Birth: __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Age: _____

Sex: Male ☐ Female ☐

3 LABORATORY TESTS

Safety measurements
__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Tests	Concentration (units)
Calcium	
Phosphate	
25(OH)D	
ALT, AST, BUN levels	
Magnesium	
Pregnancy test	
Creatinine	
GFR	
Urinalysis for hematuria	
PTH	
Albumin	

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ ___ — ___ ___ ___ ___ ___ ___

Site # Screening # Initials

Appendix 6: Week 9 form

First Name: Last name:
Home address: Phone number:

Date of Birth: __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Age: _____

Sex: Male ☐ Female ☐

4 LABORATORY TESTS

__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Test	Concentration (units)
WBC	
Hg	
Hct	
Platelets	
Ferritin	
Vitamin D	
Serological Biomarkers	
hsCRP	
Fecal Biomarkers	
Calprotectin	

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ ___ — ___ ___ ___ ___ ___

Site # Screening # Initials

Safety measurements

__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Tests	Concentration (units)
Calcium	
Phosphate	
25(OH)D	
ALT, AST, BUN levels	
Magnesium	
Pregnancy test	
Creatinine	
GFR	
Urinalysis for hematuria	
PTH	
Albumin	

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: |___|___| — |___|___|___| |___|___|___|

Site # Screening # Initials

MEASURES OF DISEASE ACTIVITY

Harvey-Bradshaw Index for Crohn's Disease

F. General Wellbeing
0=Very Well
1=Slightly below par
2=Poor
3=Very poor
4=Terrible

G. Abdominal Pain
0=None
1=Mild
2=Moderate
3=Severe

H. # Liquid Stools/Day

I. Abdominal Mass
0=None
1=Dubious
2=Definite
3=Definite and tenderness

J. Complications
1=Arthralgia
1=Erythema Nodosum
1=Aphthous Ulcers
1=Pyoderma Gangrenosum
1=Anal Fissure
1=New Fistula
1=Abscess

Total Score= _____

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ — ___ ___

Site # Screening # Initials

CROHN'S DISEASE ACTIVITY INDEX

♦ **Number of liquid or very soft stools** — **SUBTOTAL**

Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X2 =

♦ **Abdominal pain** (0=none; 1=mild, 2=moderate, 3=severe)

Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X5 =

♦ **General well-being** (0=generally well; 1-slightly under par; 2=poor; 3-very poor; 4-terrible)

Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X7 =

♦ **Number of 6 listed categories patient now has** (tick all that apply)

☐ Arthritis/Arthralgia ☐ Iritis/Uveitis ☐ Anal Fissure, Fistula or Abscess
☐ Other fistula ☐ Fever > 37.8° C during previous week
☐ Erythema Nodosum, Pyoderma Gangrenosum/Aphthous Stomatitis

Total = Total number of categories X20

♦ **Taking Lomotil/opiates for diarrhea** (tick appropriate and report total)

☐ **Yes (30)** ☐ **No (0)**

♦ **Abdominal Mass** (tick appropriate and report total)

☐ **None (0)** ☐ **Questionable (20)** ☐ **Definite (50)**

♦ **Hematocrit** (Please enter hematocrit value and calculate)

Male **(47 –** (minus) ___ **%) x 6** =

Female **(42 –** (minus) ___ **%) x 6** =

♦ **Body weight**

♦

$$= \frac{\text{Body weight}}{\text{Standard weight}} \left(1 - \frac{\text{Body weight}}{\text{Standard weight}}\right) \times 100$$

Body weight: ___ kg
Standard weight: ___ kg

Tick appropriate box
Please add (underweight) +
Or subtract (overweight) –

♦ **(Please add all subtotals)** **CDAI TOTAL**

DIETARY ASSESSMENT

First 24- dietary Hour Recall

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ — ___ ___

Site # Screening # Initials

Evening Meal				
Before Bed				

Was this intake usual? Circle one:

- ☐ Yes
- ☐ No

If No, explain why not_____

Any vitamin / mineral intake during this time?

- ☐ Yes
  if Yes, list names:

- ☐ No

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: | | | — | | | | | | | |

Site # Screening # Initials

Second 24- dietary Hour Recall

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				
Evening Meal				

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ ___ — ___ ___ ___ ___

Site # Screening # Initials

Before Bed				

Was this intake usual? Circle one:

- ☐ Yes
- ☐ No

If No, explain why not_____

Any vitamin / mineral intake during this time?

- ☐ Yes
  if Yes, list names:

- ☐ No

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: | | | — | | | | | | | |

Site # Screening # Initials

Third 24- dietary Hour Recall

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				
Evening Meal				

The impact of Vitamin D on disease activity in Crohn's disease

Week 9 Visit 3

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ ___ — ___ ___ ___ ___

Site # Screening # Initials

Before Bed				

Was this intake usual? Circle one:

- ☐ Yes
- ☐ No

If No, explain why not_____

Any vitamin / mineral intake during this time?

- ☐ Yes
  if Yes, list names:

- ☐ No

The impact of Vitamin D on disease activity in Crohn's disease

Follow-up Visit 4

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: | | | — | | | | | | |

Site # Screening # Initials

Appendix 7: Follow-up form

First Name: Last name:
Home address: Phone number:

Date of Birth: __ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Age: _____

Sex: Male ☐ Female ☐

LABORATORY TESTS

__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Test	Concentration (units)
WBC	
Hg	
Hct	
Platelets	
Ferritin	
Vitamin D	
Serological Biomarkers	
hsCRP	
Fecal Biomarkers	
Calprotectin	

The impact of Vitamin D on disease activity in Crohn's disease

Follow-up Visit 4

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: | | | — | | | | | | |

Site # Screening # Initials

Safety measurments

__ __/ __ __/ __ __ __ __ (dd/mm/yyyy)

Lab Tests	Concentration (units)
Calcium	
Phosphate	
25(OH)D	
ALT, AST, BUN levels	
Magnesium	
Pregnancy test	
Creatinine	
GFR	
Urinalysis for hematuria	
PTH	
Albumin	

Follow-up Visit 4

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ — ___ ___

Site # Screening # Initials

MEASURES OF DISEASE ACTIVITY

Harvey-Bradshaw Index for Crohn's Disease

K. General Wellbeing
0=Very Well
1=Slightly below par
2=Poor
3=Very poor
4=Terrible

L. Abdominal Pain
0=None
1=Mild
2=Moderate
3=Severe

M. # Liquid Stools/Day

N. Abdominal Mass
0=None
1=Dubious
2=Definite
3=Definite and tenderness

O. Complications
1=Arthralgia
1=Erythema Nodosum
1=Aphthous Ulcers
1=Pyoderma Gangrenosum
1=Anal Fissure
1=New Fistula
1=Abscess

Total Score= _____

The impact of Vitamin D on disease activity in Crohn's disease

Follow-up Visit 4

__ __/ __ __/ __ __ __ __
(dd/mm/yyyy)

Subject ID: ___ — ___ ___

Site # Screening # Initials

CROHN'S DISEASE ACTIVITY INDEX

	SUBTOTAL
♦ **Number of liquid or very soft stools** Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X2 =	
♦ **Abdominal pain** (0=none; 1=mild, 2=moderate, 3=severe) Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X5 =	
♦ **General well-being** (0=generally well; 1-slightly under par; 2=poor; 3-very poor; 4-terrible) Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 = Total X7 =	

♦ **Number of 6 listed categories patient now has** (tick all that apply) ☐ Arthritis/Arthralgia ☐ Iritis/Uveitis ☐ Anal Fissure, Fistula or Abscess ☐ Other fistula ☐ Fever > 37.8° C during previous week ☐ Erythema Nodosum, Pyoderma Gangrenosum/Aphthous Stomatitis Total → X20 = **Total number of categories**	
♦ **Taking Lomotil/opiates for diarrhea** (tick appropriate and report total) ☐ **Yes (30)** ☐ **No (0)**	
♦ **Abdominal Mass** (tick appropriate and report total) ☐ **None (0)** ☐ **Questionable (20)** ☐ **Definite (50)**	
♦ **Hematocrit** (Please enter hematocrit value and calculate) **Male** **(47 –** (minus) ___ **%) x 6** = **Female** **(42 –** (minus) ___ **%) x 6**	
♦ **Body weight** = Body weight / Standard weight (1 - ___ kg / ___ kg) X 100 Tick appropriate box Please add (underweight) + Or subtract (overweight) –	
♦ **(Please add all subtotals)** CDAI TOTAl	

HEALTH RELATED QUALITY OF LIFE (IBDQ)

1. How frequent have your bowel movements been during the last two weeks?

- ☐ Bowel movements as or more frequent than they have ever been
- ☐ Extremely frequent
- ☐ Very frequent
- ☐ Moderate increase in frequency of bowel movements
- ☐ Some increase in frequency of bowel movements
- ☐ Slight increase in frequency of bowel movements
- ☐ Normal, no increase in frequency of bowel movements

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

5. How much of the time during the last 2 weeks have your bowel movements been loose?

- ☐ All of the time
- ☐ Most of the time

- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

6. How much energy have you had during the last 2 weeks?
- ☐ No energy at all
- ☐ Very little energy
- ☐ A little energy
- ☐ Some energy
- ☐ A moderate amount of energy
- ☐ A lot of energy
- ☐ Full of energy

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

10. How often during the last 2 weeks have you felt generally unwell?
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time

- ☐ Hardly any of the time
- ☐ None of the time

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? please choose an option from
- ☐ A great deal of difficulty; activities made impossible
- ☐ A lot of difficulty
- ☐ A fair bit of difficulty
- ☐ Some difficulty
- ☐ A little difficulty
- ☐ Hardly any difficulty
- ☐ No difficulty; the bowel problems did not limit sports or leisure activities

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

15. How often during the last 2 weeks have you felt depressed or discouraged?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time

☐ None of the time

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas?

☐ A major problem
☐ A big problem
☐ A significant problem
☐ Some trouble
☐ A little trouble
☐ Hardly any trouble
☐ No trouble

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at.

☐ A major problem
☐ A big problem
☐ A significant problem
☐ Some trouble
☐ A little trouble
☐ Hardly any trouble
☐ No trouble

19. Many patients with bowel problems often have worries and anxieties related to their illness. these include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. in general, how often during the last 2 weeks have you felt worried or anxious?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?

☐ All of the time
☐ Most of the time

- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

21. How often during the last 2 weeks have you felt relaxed and free of tension?

- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ A good bit of the time
- ☐ Most of the time
- ☐ Almost all of the time
- ☐ All of the time

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

25. How much of the time during the last 2 weeks have you felt tearful or upset?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

28.To what extent has your bowel problem limited sexual activity during the last 2 weeks?

- ☐ 1 no sex as a result of bowel disease
- ☐ 2 major limitation as a result of bowel disease
- ☐ 3 moderate limitation as a result of bowel disease
- ☐ 4 some limitation as a result of bowel disease
- ☐ 5 a little limitation as a result of bowel disease
- ☐ 6 hardly any limitation as a result of bowel disease
- ☐ 7 no limitation as a result of bowel disease

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time

☐ None of the time

30. How much of the time during the last 2 weeks have you felt irritable?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

31. How often during the past 2 weeks have you felt a lack of understanding from others?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks?

☐ Very dissatisfied, unhappy most of the time
☐ Generally dissatisfied, unhappy
☐ Somewhat dissatisfied, unhappy
☐ Generally satisfied, pleased
☐ Satisfied most of the time, happy
☐ Very satisfied most of the time, happy

Appendix 8 : Ethics approval

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Hassanali Vatanparast	Nutrition and Dietetics	13-180

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Royal University Hospital
103 Hospital Drive

Saskatoon SK S7N 0W8

King Abdulaziz University Hospital
P.O. Box 245 Riyadh 11411
Kingdom of Saudia Arabia

SUB-INVESTIGATOR(S)
Jennifer Jones, Hani Jawa, Wael El-matary

STUDENT RESEARCHER(S)
Dania Alrefai

FUNDER(S)
SAUDI CULTURAL BUREAU

TITLE
The Impact of Vitamin D on Disease Activity in Crohn's Disease

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
03-Jul-2013	12-Aug-2013	Application for Biomedical Research Ethics Review Participant Information and Consent Form dated 9-Aug-2013 Participant Information and Consent/Assent Form dated 9-Aug-2013 Consent for the Agreement in Participation in Medical Research (Arabic version) dated 9-Aug-2013 U of S recruitment poster Arabic recruitment poster Acknowledge receipt of: Chrohn's disease activity index Socio-demographic Questionnaire Physical Activities Questionnaire Sun Exposure Questionnaire 24 Hour Recall Questionnaire Health Canada Acknowledgement Letter	11-Aug-2014

Delegated Review: ☒ Full Board Meeting: ☐

CERTIFICATION

The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. If a protocol has been reviewed at a full board meeting, a subsequent study of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8

PRINCIPAL INVESTIGATOR
Hassanali Vatanparast

DEPARTMENT
Nutrition and Dietetics

Bio #
13-180

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8

Health Canada Santé Canada

Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

Therapeutic Products Directorate

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Direction des produits thérapeutiques

NOTRE MISSION : Nous contribuons à l'amélioration de la santé des Canadiens et à l'efficacité du système de soins de santé en réglementant les produits pharmaceutiques et les matériels médicaux et en offrant aux Canadiens un accès à l'information pour qu'ils puissent faire des choix éclairés

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TO/À
Name/Nom: **Dr. Hassanali Vatanparast** Date: AUG 2 8 2013
Organization/Organisme: **College of Pharmacy and Nutrition, University of Saskatchewan**

Tel./Tél.: _____ Fax/Télécopieur: _____

No. of Pages, including this page/N° de pages, incluant cette page: 2

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Name/Nom: E-Mail/Courier électroniq _____

Tel./Tél.: Fax/Télécopieur: _____

TITLE	Manager - Clinical Trials Group I / Gestionnaire - Programme des essais cliniques Groupe I	TITRE
Division	Office of Clinical Trials / Bureau des essais cliniques	Division
Directorate	THERAPEUTIC PRODUCTS DIRECTORATE / DIRECTION DES PRODUITS THÉRAPEUTIQUES	Direction
Room	5071	Pièce
Building	Holland Cross, Tower B, 5th floor / 5 ième étage Holland Cross, Tour B	Édifice
Location	1600 Scott Street / 1600 Rue Scott	Lieu
Address Locator	3105A	Localisateur d'adresse
City/Province	OTTAWA, Ontario	Ville/Province
Postal Code	K1A 0K9	Code postal

Website/site Web : http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html/
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index_f.html

MESSAGE

Clinical Trials Manual/Manuel d'essais cliniques

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro-eng.php or /cta_intro-fra.php

Release of Protocol Safety and Efficacy Assessment Template-Clinical Trial Application (PSEAT-CTA)/
Diffusion du Modèle d'évaluation de l'innocuité et de l'efficacité des protocoles - Demande d'essai clinique (MEIEP-DEC)

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/templates-modeles/pseat_cta_meiep_dec-eng.php or /pseat_cta_meiep_dec-fra.php

Health Canada / Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

28 August 2013

9427-U0380-28C

Your file *Votre référence*

Our file *Notre référence*

Hassanali Vatanparast
Associate Professor
University of Saskatchewan
College of Pharmacy and Nutrition
110 Science Place
SASKATOON, Saskatchewan
S7N 5C9
(306) 966-6341

No Objection Letter RE: Protocol # VCD-060

Dear Dr.Vatanparast:

I am pleased to inform you that the information and material to support your Clinical Trial Application for **CHOLECALCIFEROL**, control number **166291**, received on July 29, 2013, have been reviewed and we have no objection to your proposed study. I would remind you of the necessity of complying with the *Food and Drug Regulations,* Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials. You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice.*

Please note that Health Canada has implemented electronic reporting of adverse drug reactions and is currently in pilots with some sponsors. Those sponsors who have an established electronic connection with Canada Vigilance Production stream should submit their reports using the distribution rules provided to them by Health Canada, and reporting to multiple directorates is no longer required. For the sponsors who have not yet established this connection, they should continue submitting their reports to the applicable directorate by fax or by courier. The following website provides further clarification on Health Canada's adverse drug reactions reporting requirements for clinical trials: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.pdf

Consistent with Health Canada's Notice - *Registration and Disclosure of Clinical Trial Information* of November 30, 2007, sponsors are encouraged to register their clinical trials within 21 days of the trial's onset, using a publicly available registry that conforms with international standards for registries such as: Clinicaltrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com).

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

LB/en

Canada

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Hassanali Vatanparast	Nutrition and Dietetics	13-180

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Royal University Hospital
103 Hospital Drive
Saskatoon SK S7N 0W8

King Abdulaziz University Hospital
P.O. Box 245 Riyadh 11411
Kingdom of Saudia Arabia

SUB-INVESTIGATOR(S)
Jennifer Jones, Hani Jawa, Wael El-matary

STUDENT RESEARCHER(S)
Dania Alrefai

FUNDER(S)
SAUDI CULTURAL BUREAU

TITLE
The Impact of Vitamin D on Disease Activity in Crohn's Disease

RE-APPROVED ON
10-Jul-2014

EXPIRY DATE
09-Jul-2015

Delegated Review ☒ Full Board Meeting ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This re-approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This re-approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8

Saskatoon Health Region

UNIVERSITY OF SASKATCHEWAN

Associate Vice-President Research – Health
(University of Saskatchewan)
Vice-President Research and Innovation
(Saskatoon Health Region)
Room A102, Health Sciences Building
107 Wiggins Road, University of Saskatchewan
Saskatoon, SK S7N 5E5
Phone: (306) 966-8745

DATE: **March 19, 2014**

TO: **Dr. Hassanali Vatanparast**
College of Pharmacy and Nutrition
University of Saskatchewan

FROM: Martha E. (Beth) Horsburgh
Associate Vice-President Research – Health (University of Saskatchewan)/
Vice-President Research & Innovation (Saskatoon Health Region)

RE: **RESEARCH ETHICS BOARD (REB) #: BIO-13-180**
PROJECT NAME: The Impact of Vitamin D on Disease Activity in Crohn's Disease
PROTOCOL #: N/A

Saskatoon Health Region is pleased to provide you with operational approval of the above-mentioned research project.

Kindly inform us when the data collection phase of the research project is completed. We would also appreciate receiving a copy of any publications related to this research. As well, any publications or presentations that result from this research should include a statement acknowledging the assistance of Saskatoon Health Region.

We wish you every success with your project. If you have any questions, please feel welcome to contact Shawna Weeks at 655-1442 or email shawna.weeks@saskatoonhealthregion.ca

cc: Karen Nogier, Laboratory Medicine, RUH
Leslie Worth, Senior Manager, IBD Clinic - CDM, RUH

Catalyzing Health Research and Innovation Together

Associate Vice-President Research – Health
(University of Saskatchewan)
Vice-President Research and Innovation
(Saskatoon Health Region)
Room A102, Health Sciences Building
107 Wiggins Road, University of Saskatchewan
Saskatoon, SK S7N 5E5
Phone: (306) 966-8745

DATE: **July 21st, 2014**

TO: **Dr. Hassanali Vatanparast**
College of Pharmacy and Nutrition
University of Saskatchewan

FROM: Martha E. (Beth) Horsburgh
Associate Vice President Research – Health (University of Saskatchewan)/
Vice-President Research & Innovation (Saskatoon Health Region)

RE: **RESEARCH ETHICS BOARD (REB) #: BIO-14-161**
PROJECT NAME: The Impact of Vitamin D on Disease Activity in Crohn's Disease
PROTOCOL #: VCD-060

Saskatoon Health Region is pleased to provide you with operational approval of the above-mentioned research project.

Kindly inform us when the data collection phase of the research project is completed. We would also appreciate receiving a copy of any publications related to this research. As well, any publications or presentations that result from this research should include a statement acknowledging the assistance of Saskatoon Health Region.

We wish you every success with your project. If you have any questions, please feel welcome to contact Shawna Weeks at 655-1442 or email shawna.weeks@saskatoonhealthregion.ca

cc: Dr. Jennifer Jones, Medical Director, IBD Clinic, RUH

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Hassanali Vatanparast	Nutrition and Dietetics	14-161

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Royal University Hospital
103 Hospital Drive
Saskatoon SK S7N 0W8

SUB-INVESTIGATOR(S)
Jennifer Jones

STUDENT RESEARCHER(S)
Dania Alrefai

FUNDER(S)
Saudi Cultural Bureau

TITLE
The Impact of Vitamin D on Disease Activity in Crohn's Disease

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
23-Jun-2014	10-Jul-2014	Revised Application to Access Existing Health Data for Research, submitted July 9 2014 Revised Data Collection Tool submitted July 9 2014 Master List Acknowledge receipt of: McMaster certificate for Dania Alrefai	09-Jul-2015

Delegated Review ☒ Full Board Meeting ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. If a protocol has been reviewed at a full board meeting, a subsequent study of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval

Please send all correspondence to:
Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8

PRINCIPAL INVESTIGATOR
Hassanali Vatanparast

DEPARTMENT
Nutrition and Dietetics

Bio #
14-161

and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

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Appendix 9: Poster

How does *vitamin D* affect disease activity in Crohn's disease?

Participants Needed for Research Study

What is measured?

Vitamin D & biomarkers

Diet and physical activity status

Who?

Crohn's disease patients who:

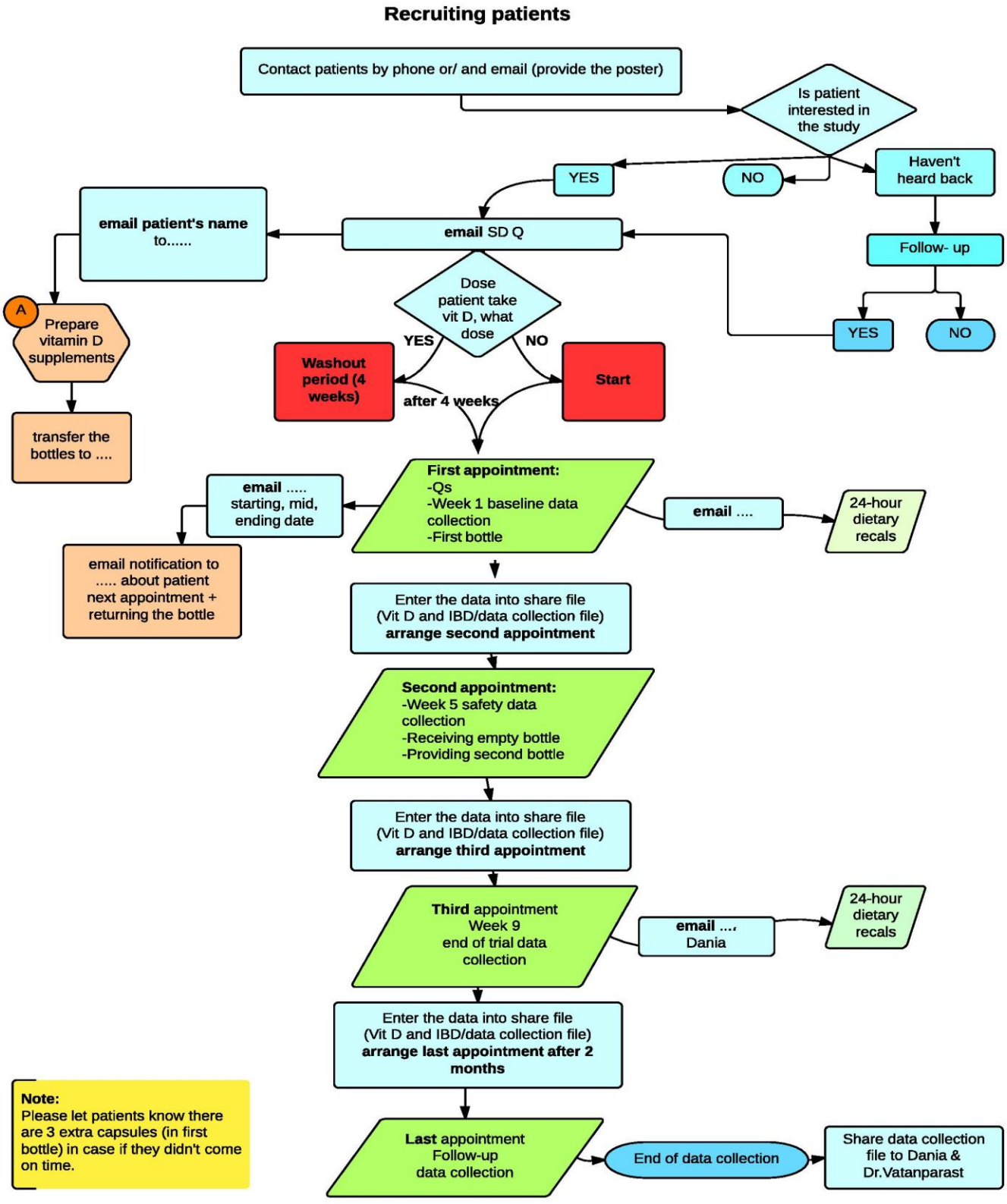
- Were diagnosed 2 years ago or less
- Are 16 years and above
- Are not pregnant
- Do not have liver or kidney failure
- Are not taking corticosteroids
- Have the ability to take oral supplements/ medicine

Involves 1 visit (1 hour) per month over 4 months

Contact Information

UNIVERSITY OF SASKATCHEWAN

Appendix 10: Recruiting patients flow charts



Steps to prepare vitamin D supplements for CD patients

Appendix 11

Table 4.1 Socio –Demographics characteristics

Case	Location	Age	Sex	BMI	no. of individual living at home	no. of children living at home	languages	Highest grade of education	Total income (per year)
Case 1 (withdrew)	Saskatoon	60	F	25.3	-	-	English, French	-	-
Case 2	Riyadh	25	M	22.9	10	2	Arabic	Bachelor	$25,000 to < $30,000
Case 3	Riyadh	21	F	17.9	7	0	Arabic	Bachelor	$20,000 to < $25,000
Case 4 (Missing follow up)	Riyadh	19	F	16.9	8	6	Arabic, English	High school	-
Case 5	Saskatoon	32	F	29	3	1	English	< Grad 8	$60,000 to < $80,000
Case 6 (Missing follow up)	Saskatoon	35	M	23.4	-	-	English	-	-
Case 7	Riyadh	25	M	22.8	11	4	Arabic	Bachelor	$20,000 to < $25,000
Case 8	Riyadh	28	M	23	4	2	Arabic	Bachelor	$30,000 to < $40,000
Case 9	Riyadh	24	M	18.3	-	-	Arabic, English	Bachelor	$60,000 to < $80,000

Table 4.5 Food Groups Dietary Usual Intake and Healthy Eating Index Indicators

Case	HEI		Intake of Food groups															
			Baseline								week 9							
	Baseline	Week 9	Meat and Alternatives	Milk and Alternatives	Grain Products	Whole Grains	Vegetables and Fruits	Dark Green and orange vegetables	Whole fruit (servings)	others (%kcal)	Meat and Alternatives	Milk and Alternatives	Grain Products	Whole Grains	Vegetables and Fruits	Dark Green and orange vegetables	Whole fruit (servings)	others (%kcal)
Case 1	65.1	61.6	2.0	1.3	2.3	0.3	3.3	1.7	1.8	15.6	2.3	0.4	3.8	0.9	4.1	1.7	2.0	27.5
Case 2	28.5	55.5	1.3	0.5	5.3	0	2.2	0.3	0.2	34.5	2.0	0.5	5.9	0	2.5	0.6	0	12.3
Case 3	40.6	34.0	1.4	0.6	6.0	0	0.7	0.1	0	40.8	2.2	0.6	3.4	0	0.8	0	0	47.9
Case 4	30.3	-	1.6	0.6	5.1	0	0.2	0	0	34.5	-	-	-	-	-	-	-	-
Case 5	69.4	73.5	1.4	2.9	5.2	2.2	6.0	0.8	3.8	15.3	2.0	1.8	3.8	0.8	4.3	0.6	2.6	15.9
Case 6	37.7	57.0	1.2	1.7	5.3	1.0	4.3	1.0	1.3	33.6	1.3	1.4	8.2	6.1	0.9	0	0.3	9.4
Case 7	50.3	36.5	4.6	0.1	3.0	0	1.8	0.1	0	16.9	1.9	0.8	3.2	0	0.8	0	0	38.9
Case 8	48.2	41.1	3.6	0.2	4.4	0.3	1.9	0.2	0	7.9	2.5	0.6	3.8	0	1.3	0	0	34.0
Case 9	39.8	35.6	2.3	0.4	4.3	1.5	0.3	0	0	33.3	1.3	1.1	3.8	0	0.9	0.2	0.1	29.4

Table 4.6 Disease Related Information Data

Case	Disease location at enrolment	Disease behavior at enrolment	Perianal disease at enrolment	Past medication/ supplements	Current medication	Surgical history	Family History IBD-Associated Conditions	Extra-intestinal-manifications
Case 1	-	-	-	Probiotic	None	No	Sibling (PSC), parent (eczema), second degree (colon cancer)	None
Case 2	++small bowel (Jejunum), ++ colon (ascending, transverse, descending, sigmoid)	-	none	5-ASA Azathioprine	5-ASA Azathioprine	No	Sibling (Eczema)	None
Case 3	++small bowel , ++ colon (ascending, transverse, descending,rectum)	Inflammatory	none	Azathioprine	Azathioprine Adalimumab	No	none	None
Case 4	-	Inflammatory Penetrating	Perianal Fistula	Azathioprine	Azathioprine	No	none	None
Case 5	*++small bowel (terminal lleum, ileocecal valve), +– colon (cecum, ascending, transverse, descending, sigmoid)	Inflammatory	none	multivitamin	Budesonide Infliximab	No	Second degree (Eczema, colon cancer)	None

Case 6	++small bowel (terminal lleum, ileocecal valve), +– colon (cecum, ascending, transverse, descending, sigmoid)	-	-	Azathioprine	Budesonide	ileum	Parent, sibling (asthma), sibling, children (eczema)	None
Case 7	–Small bowel (terminal lleum)	Inflammatory	Perianal Abscess	5-ASA Infliximab	Infliximab	No	none	None
Case 8	++small bowel , ++ colon (sigmoid, rectum)	Inflammatory	none	Azathioprine	Azathioprine Adalimumab	No	none	None
Case 9	+– small bowel, ++ terminal lleum	Inflammatory	none	Azathioprine	Azathioprine	No	none	None

* Bowel+, inflam +, Bowel+, inflam –, Bowel– or unknown

Appendix 11

Table 4.7 Laboratory and Safety Measurements at Baseline

Case	WBC (10.e9/L)	Hbg (g/L)	Hct %	Platelets (10.e9/L)	Ferritin (ug/L)	Calcium (mm/L)	Phosphate (mm/L)	ALT Levels (U/L)	AST levels (U/L)	BUN levels (U/L)	Magnesium (mmol/L)	Creatinine (umol/L)	GFR (mL/min)	Urinalysis for hematuria (try/ul)	PTH (PM/L)	Albumin (g/L)
Case 1	6.8	127	38.4	341	35	2.3	1.2	14	13	7.8	0.7	57	-	0	4.3	37
Case 2	4.3	146	42.9	311	65.4	2.2	-	38	21	-	0.8	71	-	0	5.3	42.4
Case 3	4.5	126	37.3	315	19.1	2.1	-	26	14	-	0.8	49	-	0	16.8	38
Case 4	11.4	101	31.3	385	35.1	2.2	-	25	11	-	0.8	47	-	0	-	33
Case 5	10.9	115	34.7	300	-	2.2	1.0	18	14	2.8	-	66	106	10	3.2	33
Case 6	6.1	147	42.3	356	122	-	-	10	21	4.9	-	76	114	-	-	-
Case 7	6.9	162	48.7	192	190.2	2.1	-	44	26	-	0.8	93	-	0	1	36
Case 8	6.6	145	42.1	228	134.9	2.2	-	49	26	-	0.8	81	-	-	2.9	43
Case 9	9.3	155	44.9	262	74.6	2.2	-	31	21	-	0.8	63	-	0	7.8	36

Table 4.8 Laboratory and Safety Measurements at Week 5

Case	Calcium (mm/L)	Phosphate (mm/L)	ALT Levels (U/L)	AST levels (U/L)	BUN levels (U/L)	Magnesium (mmol/L)	Creatinine (umol/L)	GFR (mL/min)	Urinalysis for hematuria (try/ul)	PTH (PM/L)	Albumin (g/L)
Case 1	2.4	1.5	22	20	8.1	0.6	50	101	0	2.4	29
Case 2	2.3	-	26	19	-	0.8	65	-	0	5.3	41
Case 3	2.1	-	27	13	-	0.8	49	-	0	6.9	36
Case 4	2.2	-	24	7	-	0.8	55	-	0	17.2	33
Case 5	2.1	1.1	11	13	3.4	0.7	65	108	0	4.7	30
Case 6	2.3	1.1	13	21	4.1	0.7	73	116	10	-	37
Case 7	2.2	-	41	22	-	0.9	80	-	0	1.4	39
Case 8	2.2	-	49	26	-	0.8	81	-	-	3.8	43
Case 9	2.3	-	27	22	-	0.8	65	-	0	8	42

Table 4.9 Laboratory and Safety Measurements at Week 9

Case	WBC (10.e9/L)	Hbg (g/L)	Hct %	Platelets (10.e9/L)	Ferritin (ug/L)	Calcium (mm/L)	Phosphate (mm/L)	ALT Levels (U/L)	AST levels (U/L)	BUN levels (U/L)	Magnesium (mmol/L)	Creatinine (umol/L)	GFR (mL/min)	Urinalysis for hematuria (try/ul)	PTH (PM/L)	Albumin (g/L)
Case 1	10.0	132	41.1	388	145	2.6	1.5	41	55	6.6	0.6	46	104	10	2	34
Case 2	7.9	138	40.4	295	73.8	2.2	-	30	20	-	0.8	65	-	0	5.6	44
Case 3	5.1	117	35.5	372	21.4	2.1	-	25	12	-	0.8	65	-	0	15.8	34
Case 4	12.8	107	33.1	340	35.1	2.2	-	26	10	-	0.8	67	-	0	17.2	35
Case 5	11.1	118	36.6	340	-	2.1	1	9	12	2.7	0.7	64	110	0	3.6	29
Case 6	5.9	156	44	310	87	2.2	0.9	10	18	5.4	0.8	84	105	0	2.2	33
Case 7	8.7	163	47.6	279	228.7	2.2	-	79	91	-	0.8	83	-	0	1.4	37
Case 8	8.2	156	45.8	217	134.9	2.2	-	53	29	-	0.8	91	-	0	3.8	41
Case 9	6.5	156	45.2	279	76.0	2.3	-	27	20	-	0.8	71	-	0	8	39

Table 4.10 Laboratory and Safety Measurements at Follow-up

Case	WBC (10.e9/L)	Hbg (g/L)	Hct %	Platelets (10.e9/L)	Ferritin (ug/L)	Calcium (mm/L)	Phosphate (mm/L)	ALT Levels (U/L)	AST levels (U/L)	BUN levels (U/L)	Magnesium (mmol/L)	Creatinine (umol/L)	GFR (mL/min)	Urinalysis for hematuria (try/ul)	PTH (PM/L)	Albumin (g/L)
Case 1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Case 2	4.2	126	36.9	312	81.0	2.3	1.0	28	19	-	1	70	-	0	6.4	40
Case 3	5.5	105	32.6	11.9	9.8	2.1	1.2	30	14	-	0.9	60	-	0	26.8	32
Case 4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Case 5	6.6	117	35.3	267	55	2.1	1.2	17	-	3.4	0.8	68	102	10	4	33
Case 6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Case 7	8.8	163	47.6	300	200	2.3	1	79	91	-	0.8	70	-	0	1.4	37
Case 8	8.1	154	45.3	231	192.5	2.2	1.1	37	-	-	0.8	90	-	0	3.5	42
Case 9	6.9	167	47.4	272	104	2.3	1.3	25	17	-	0.8	71	-	0	3.1	38