Summer 2019

Vitamin D Status in Gastrointestinal Disease and Hepatic Disorders

Allison Peters
allisonpeters2@gmail.com

Vitamin D Status in Gastrointestinal and Hepatic Disorders

Allison Peters, RD

In partial fulfillment of requirements for Masters of Family and Consumer Sciences in Dietetics

Iowa State University

July 9, 2019

ABSTRACT

Background:

Over the last decade, it is estimated that Vitamin D insufficiency has increased. Currently, approximately 50% of the population has Vitamin D deficiency, including all ages and ethnicities (Nair, 2012). This change is thought to be partially due to behavior changes; such as less time spent outside, as well as an increase in the use of sunscreen while outside (Nair, 2012). Vitamin D insufficiency is defined as a serum vitamin D level between 21-29 ng/mL of 25-hydroxyvitamin D [25(OH)D] (Nair,2012). Vitamin D deficiency is defined as a serum vitamin D level </= 20ng/mL of 25-hydroxyvitamin D [25(OH)D] (Nair, 2012).

Purpose:

The purpose of this research is to determine if there is adequate Vitamin D status (25-hydroxyvitamin D [25(OH)D] >30 ng/mL) in patients with various gastrointestinal disorders; such as inflammatory bowel disease, liver disease, bowel resection, as well as those requiring parenteral nutrition following surgical resection or malabsorption issues. Low Vitamin D status may be a marker of increased risk for bone fractures, poor wound healing and other complications. A review of the literature will be conducted to summarize the evidence. This evidence will be used to educate providers, dietitians, diet technicians and dietetic interns on the importance of adequate Vitamin D status, and the connections to decline of health and function. The overall intent is to raise awareness of Vitamin D status and health outcomes in patients with GI disorders and the importance of adequate Vitamin D status.

Methods:

Literature was gathered by online library search using the PubMed database and Google Scholar. Using identified inclusion and exclusion criteria 26 studies were used and reviewed. The

studies were then graded using the Academy of Nutrition and Dietetics Evidence Analysis Worksheet.

Results:

Patients with gastrointestinal disorders were at a higher risk of Vitamin D deficiency and should be monitored for Vitamin D status. Supplementing with oral Vitamin D alone or Vitamin D supplied in multivitamin form is recommended to maintain adequate Vitamin D status. Patients with Crohn's disease were at higher risk for Vitamin D deficiency and should be monitored closely. Currently, IV Vitamin D is not available in the United States. Individuals relying solely on parenteral nutrition, are usually only receiving 400IU of vitamin D from the multivitamin provided within the parenteral infusion. UV light may be another option to be explored for those that cannot absorb vitamin D orally.

Conclusion:

1) Vitamin D status should be obtained in patients with Crohn's disease, ulcerative colitis, short gut syndrome and other bowel resection surgeries, liver disease as well as those on parenteral nutrition with malabsorption disorders, to determine if deficiency or insufficiency is present. 2) Supplementation should be determined per protocol at each facility.

Introduction

Vitamin D is a fat-soluble vitamin that the body is able to produce with sunlight exposure but is also derived from dietary intake (Palacios, et al., 2014). Vitamin D plays an important role in the human body to maintain bone structure, growth and mineral metabolism. The primary function of Vitamin D is to regulate calcium absorption and maintain homeostasis. Sun exposure is needed for ultraviolet-B (UVB) induced Vitamin D production to occur in the skin. A healthy adult after a day at the swimming pool during summer months may produce enough vitamin D to equal a supplementation of 10,000 to 25,000 IU (Nair,2018). Although skin pigmentation, application of sunscreen, and age are factors that may limit this process and vary per individual (Nair,2018). The intensity of UVB exposure depends on latitude, season, time of day and skin exposure.

The highest source of naturally occurring dietary Vitamin D is in fatty fish such as salmon, tuna, mackerel, and fish liver oil. Smaller amounts of vitamin D are found in cheese, beef liver, egg yolks, and some mushrooms. Fortified milk and cereals are a prime source of vitamin D in the United States (Shils, 2006).

Synthesis of Vitamin D in the skin is initiated with exposure to ultraviolet-B (UVB light). Synthesis begins with 7-dehydrocholesterol (7-DHC) which both the outer layers of the skin, the epidermis and the dermis, contain. The outer skin layers absorb UVB photons that are converted to cholecalciferol or vitamin D3 (Bickle, 2014). Cholecalciferol is produced in a two-step process in which photoisomerization of UVB light and the vitamin precursor B ring forms pre-cholecalciferol in the upper layers of the skin. It then undergoes heat sensitive and spontaneous isomerization to form the vitamin D3 molecule, cholecalciferol in the lower layers of the skin (Bickle, 2014).

Once cholecalciferol is produced, it is transported for storage in the adipose tissue or the liver to be metabolized via chylomicrons. Once it is in circulation it binds to the Vitamin D binding protein and it is released into the liver. The liver converts cholecalciferol to 25-hydroxyvitamin D [25(OH)D] by hydroxylation of the carbon molecule on the 25 position to a hydroxyl group via the catalyst 25-hydroxylase, in the hepatocytes creating 25-hydroxycholecalciferol (calcifediol or 25(OH)D) (Bikle,2007). The hepatocytes then express calcifediol into the plasma where it is bound to an α-globulin carrier, Vitamin D-binding protein (Christakos, et al., 2017).

Calcifediol is transported to the proximal tubules of the kidneys where the expression of the enzyme 1-alpha-hydroxylase works with cubulin and megalin, other proteins that are expressed within the renal tubule and forms the active metabolite, calcitriol (1,25-dihydroxycholecalciferol, 1,25(OH)2D) (Bikle,2007). Calcitriol then enters the circulation and is distributed throughout the body and organs by binding to the Vitamin D receptor (Bikle, 2007). It then has two major functions within the body, to increase intestinal calcium and phosphorus absorption and ensure osteoclasts become mature from preosteoclasts (Battault, et al, 2012).

Calcitriol or 1,25 dihydroxyvitamin D function is to maintain calcium and phosphate homeostasis. Calcitriol elevates serum calcium levels to within normal range via three mechanisms (Shils, 2006); 1) Directly stimulating intestinal calcium absorption throughout the intestine and indirectly stimulating phosphate absorption (Shils, 2006); 2) Mobilization of calcium from the bone by activating osteoclast formation using parathyroid hormone (Shils, 2006); and 3) Calcitriol and parathyroid hormone stimulate reabsorption of calcium within the distal tubule in the kidney (Shils, 2006).

When there is a low serum calcium level, parathyroid hormone (PTH) regulates an increase in 1-alpha hydroxylase by increasing CYP27B1 gene expression inside the kidney (Shils,

2006). When Vitamin D deficiency is present, there is an increase in 1-alpha hydroxylase (Shils, 2006). When deficiency of Vitamin D is not present, the presence of 1-alpha hydroxylase is suppressed causing a negative feedback effect (Shils, 2006).

Increased parathyroid hormone which can be caused by a rise in serum calcium concentration and a fall in phosphorus will stimulate 1,25 dihydroxyvitamin D production and inhibit parathyroid hormone secretion (Shils, 2006). Vitamin D receptors on the cell surface may be down regulated playing a role in Vitamin D activation (Shils, 2006).

Vitamin D Receptors (VDR) are nuclear receptor which the metabolite of vitamin D, calcitriol, activating the VDR (Moore, et al., 2006). After activation VDR dimerizes with the retinoid X receptor creating a complex that acts as a transcription factor for gene expression for transport proteins. These transport proteins are involved in calcium absorption in the intestine (Moore, et al., 2006) and a variety of other metabolic pathways including inhibiting growth of cancer cells and immune response (Adorini, et al., 2006). VDRs can be expressed by cells in the brain, heart, skin, as well as breast and gonads (Dusso, 2011). Activation of VDR in the bone, intestine, kidney and parathyroid gland cells regulate calcium and phosphorus in the blood and bone maintenance along with parathyroid hormone and calcitonin (Dusso, 2011). VDR also regulates cell differation and proliferation (Puccetti, et al, 2002).

Vitamin D is absorbed in the intestine, via the jejunum and ileum by way of the portal and lymphatic system (Bickle, 2007). When vitamin D is ingested through diet in the form of fatty fish, fish liver oil, egg yolks or fortified foods, it is emulsified into lipids within the stomach and duodenum (Reboul, 2015). The fat-soluble compound enters the lipoprotein fraction and then can be absorbed into the lymphatic system. It is then absorbed in the proximal small bowel, appears to be more rapid in the duodenum and quickly converted to 25-OHD in the liver (Mueller, 2012). Bile salts are required for Vitamin D absorption for solubilization in the micelle

(Shils, 2006). When the production of bile salts is impaired, absorption of Vitamin D can be impaired as well (Shils, 2006). Once solubilization has occurred it is then delivered to the enterocyte apical membrane and passively diffused within the enterocytes which then form into chylomicrons for absorption into the lymphatic system and then to the bloodstream (Shils, 2006).

Without proper Vitamin D status, demineralization of bone can occur in adults, leading to a condition called osteomalacia. Without adequate Vitamin D status, a decrease in the body's ability to absorb calcium and phosphorus from diet occurs. A decrease in calcium and phosphorus within the body then increases parathyroid hormone which increases osteoclast activity leading to bone weakness and decreased bone density (Nair, 2018). Osteomalacia can soften bones causing bones to become weakened and may bend or break, increasing risk of falls and fracture which can increase the number of hospitalizations (Nair, 2018; Meehan, et al., 2014; Jiang, 2018).

It is thought Vitamin D status can play a role in many chronic diseases and increasing research is emerging (Meehan, et al., 2014) suggesting an association among vitamin D deficiency and osteoporosis, cognitive function, cardiovascular disease, diabetes, hypertension, cancer, mortality, depression, and increasing healthcare costs (Autier,2019; Nair,2018; Jiang, 2018). Studies are suggesting negative outcomes with lower Vitamin D status and chronic disease and an increased risk for mortality and increased healthcare costs (Mckinney, 2011).

Currently, the deficiency of Vitamin D in the human population is a pandemic that is not well recognized (Mckinney, 2011). It is estimated that 50% of the world's population is affected by Vitamin D insufficiency (Nair, 2018) and nearly 1 billion people worldwide have deficient or insufficient Vitamin D status (Pfotonhauer, et al., 2017). Vitamin D insufficiency was also found in countries with low latitudes which generally are exposed to adequate sunlight as well as

industrialized countries which generally fortify foods to provide a higher intake of dietary Vitamin D (Palacios, et al., 2014). Vitamin D insufficiency affects males and females, all ethnicities, all age groups and estimated to affect one billion people (Palacios, et al.,2014). It is hypothesized that due to less outdoor exposure to sunlight and the use of sunscreen likely contribute to the rise in Vitamin D deficiency (Nair, 2012). As a person ages, their risk of Vitamin D deficiency increases, older adults (age >65) with Vitamin D deficiency was found to range from 20-100% in the United States alone (Meehan, et al.,2014). This may be related to less time spent outside or a decline in intakes of Vitamin D sources of food. Other factors that may play a role in Vitamin D status may include increased adipose tissue or decreased synthesis of Vitamin D in the body (Meehan, et al.,2014).

There are certain population groups who are at higher risk of Vitamin D deficiencies as including those who are homebound or spend little time outdoors, use sunscreen daily, live in higher latitudes, have darker skin tone, are overweight/obese, who are 60 years and older, have intestinal malabsorption disorders, and infants that are exclusively breast fed.

The metabolite 25-hydroxyvitamin D [25(OH)D] is usually used as a lab marker to determine the Vitamin D status due to its reflection of Vitamin D from all sources (sunlight and diet) and has a half-life of 2-3 weeks. The active form of Vitamin D (1,25(OH)2D has a half-life of 4 hours. Vitamin D Status is determined by the laboratory value Serum 25-hydroxyvitamin D (25(OH)D). See Table 2 for recommendation of serum Vitamin D levels and Table 1 for recommended intakes based on age.

Vitamin D requirements depend upon a person's age. Requirements are the same for males and females.

Table 1 Vitamin D recommendations ("Office of Dietary Supplements - Vitamin D").

Age	**Recommendation**
0-12 months	400 IU
1-13 years	600 IU
14-18 years	600 IU
19-50 years	600 IU
51-70 years	600 IU
>70 years	800 IU
Pregnancy or Lactation	600 IU

Table 2 Recommended serum 25-Hydroxyvitamin D levels ("Office of Dietary Supplements - Vitamin D").

nmol/L	**ng/mL**	**Health Related**
< 30	< 12	Vitamin D deficiency Osteomalacia in adults
30 to < 50	12 to < 20	Inadequate for bone health and general health in healthy individuals
>50	>20	Adequate for bone health and general health of healthy individuals
>125	>50	May have adverse effects with high levels

While it is known that Vitamin D has an important role in skeletal health, Vitamin D absorption can be affected by disorders of the intestine, liver disease or bowel surgical interventions which can result in malabsorption of Vitamin D, as well as calcium and phosphorus and lead to osteoporosis (Bickle, 2007). Gastrointestinal diseases that contribute to known malabsorption of Vitamin D include bowel disorders and surgeries such as post-gastrectomy, celiac disease, inflammatory bowel disease, pancreatic insufficiency, short gut syndrome, and bariatric surgery. Inflammatory bowel disease and Vitamin d deficiency may be linked by immunological effects (Neilson, 2019). As Inflammatory bowel disease consists of inflammation and ulceration of the gastro-intestinal tract and Vitamin D has been recognized for an important role in gut mucosal immunity regulation (Fletcher et al., 2019). Studies suggest Vitamin D has a role protecting gut epithelial integrity, T cell development and function, promoting anti-inflammatory cytokines and innate immune barrier function (Fletcher et al., 2019). Vitamin D is thought to have a direct effect on the immune system due to its role in T cell development and function (Mudambi, 2018). Vitamin D receptors play a role of being able to mitigate intracellularly and activating cytokines and while being found to express within cells that comprise the immune system, such as T cells and macrophages (Mudambi, 2018). Vitamin D promotes synthesis of Interleukin 10 (IL-10) which is an anti-inflammatory cytokine and plays a role in the development of Inflammatory bowel disease (Mudambi, 2018). IL-10 also plays an important role as an anti-inflammatory cytokine that is secreted by macrophages, monocytes and epithelial cells which then can release the pro-inflammatory cytokine TNT-*a* (Mudambi, 2018). TNT-*a* causes IL-10 to inhibit CD 4 T cells expression and cause an inflammatory response in Inflammatory bowel disease (Mudambi, 2018).

Furthermore, hepatic disease may also contribute to Vitamin D deficiency due to cirrhosis, hepatitis (chronic, alcoholic and viral) and those that are status post liver transplant (Bickle, 2007). Bowel diseases that affect the small bowel distally as well as the large intestine can alter absorption of Vitamin D (Shils,2006). This is an area that is beginning recently to be investigated and may need more research and awareness in the future.

Statement of Purpose

The purpose of this review of the literature is to determine adequate Vitamin D status (25-hydroxyvitamin D [25(OH)D] >30) in gastrointestinal disorders such as inflammatory bowel disease, intestinal failure, patients on parenteral nutrition and bowel resections due to possible reduced ability to absorb vitamin D. The review of literature will summarize the research in this area to better inform providers, dietitians, dietetic technicians and dietetic interns on the importance of monitoring Vitamin D status in patients with gastrointestinal and liver disorders, with the goal of preventing secondary health consequences. The overall intent is to raise awareness of Vitamin D status and health outcomes and the importance of adequate Vitamin D status in hospital clinicians.

Objectives

1. To review the literature relative to Vitamin D status in patients with gastrointestinal disorders and if they are at risk for Vitamin D deficiency.
2. To develop educational materials to assist healthcare providers in understanding the role of Vitamin D status in health outcomes.

Specific Aims

1. To conduct a literature review to determine the usefulness of routinely checking for adequate Vitamin D status in patients with a history of gastrointestinal disorders both disease related and surgical. It is assumed that Vitamin D levels are not generally checked in an acute setting unless there is a history of deficiency.
2. To evaluate the correlation between Vitamin D status and malabsorption in gastrointestinal disorders.
3. To establish evidence to be used to educate healthcare providers.
4. To determine if there is a relationship between negative outcomes of skeletal health in patients and gastrointestinal disorders.
5. To determine if adequate Vitamin D status improve outcomes in patients with gastrointestinal disorders?

Approach to meeting specific aims

The guidelines developed by the Academy of Nutrition and Dietetics will be used to perform the "Evidence Based Analysis" process for this project.

Step 1: Develop a Question

This question was developed as a focus for my creative component. I am a clinical inpatient dietitian with an interest in acute care, where many patients suffer from gastrointestinal disorders. I would like to learn more about the role of Vitamin D and bowel disease and bowel surgeries that can affect hospitalized patients.

Step 2: Gather and Classify Research

Methods- Literature Search

Research articles were gathered from online databases, PubMed and Google Scholar. Reviewed 60 abstracts and introductions to determine if met inclusion criteria. Many were duplicates or did not meet criteria, unfortunately, many studies in this area involved pediatrics or rodents, 26 full text articles were reviewed (Table 3). Position papers from the academy were also reviewed. Reviewed articles using AND evidence analysis manual (Appendix 1).

The following keywords were used to find articles pertinent: vitamin d and gastrointestinal disease, vitamin d status, vitamin d and drug interactions, vitamin d and liver disease, vitamin d status in intestinal surgeries, vitamin d and long-term parental nutrition, vitamin d and intestine failure, vitamin d and surgical patients

Table 3 - Criteria used for Literature Search

Inclusion Criteria	**Exclusion Criteria**
Adult aged 18 years old and older	Youth under < 18 years
Serum vitamin D <30ng/mL	Subjects with only adequate Vitamin D levels
Gastrointestinal disease (chronic, surgical and liver disease)	Studies published over 10 years ago
Studies published in the last 10 years	Studies not in the English language
English language	Studies that do not involve human subjects
Human subjects	

A presentation with findings will be given to an interdisciplinary team to create awareness of monitoring Vitamin D levels in patients with gastrointestinal disorders. Feedback will be requested in the form of a survey. IRB approval was not indicated as this is considered a quality improvement effort.

Table 4 Summary of Articles Reviewed
Grading of articles see appendix 1

Citation& Grade	Study Purpose	Study Population	Methods	Outcomes	Conclusions	Limitations
Parenteral Nutrition						
Thomson, Patti, and Donald R. Duerksen. "Vitamin D Deficiency in Patients Receiving Home Parenteral Nutrition". Journal of Parenteral and Enteral Nutrition, vol 35, no. 4, 2011, pp. 499-504. Wiley, doi:10.1177/0148607110381269. Grade I	Measure 25(OH)D levels in patients enrolled in a provincial HPN program to determine adequacy of vitamin D supplementation.	Adult patients on home TPN for >1 month in the Monitoba Home Nutrition Program. 22 patients qualified for this study. June 2008 to July 2009	25(OH)D was measured along with phosphorus, mg and ionized calcium. Diet recall was looked at to determine dietary vitamin D intake by diet analysis by anRD. 24hour diet recall. All patients received IV MVI that contains 200 IU vit D3. Vit D def <50nmol/L (20ng/mL) and insufficiency >50nmol/L but <75 nmol/L (30 ng/mL).	Reasons for TPN gastrointestinal dysmotility (45%) malabsorption/short bowel syndrome (36%). GI obstruction (18%). Deficiency was present in 15 patients and insufficiency was present in 6 patients. 1 patient was not deficient and was taking 2000IU d3 in addition to IV MVI. There was no correlation	In this study a high prevalence of vitamin D insufficiency/ deficiency was found in patients receiving home TPN. All patients that were not receiving additional supplements had serum levels in the subnormal range. Exposure to sunlight may be limited in HPN due to underlying conditions limiting time spent outside.	The clinical impact of deficiency and optimal supplemental dose of replacement require further study.

				found in intestinal length with those with short bowel syndrome. All patients had normal ca, phos levels at time of vit d assessment	Also at risk due to GI disorders that limited intestinal absorption. Vit D should be routinely supplemented and 25(OH)D levels monitored.	
Bharadwaj, Shishira et al. "Prevalence and Predictors of Vitamin D Deficiency And Response To Oral Supplementation In Patients Receiving Long-Term Home Parenteral Nutrition". Nutrition in Clinical Practice, vol 29, no. 5, 2014, pp. 681-685. Wiley, doi:10.1177/0884533614539178. Grade I	Determine the prevalence and predictors of vitamin D deficiency in long term home TPN patients	79 patients met eligibility criteria. Eligible patients were classified by mean serum vitamin D. Sufficient:>30ng/mL Insufficient:20-30ng/mL Deficient:<20ng/mL Inclusion- adult patients on HPN >6 months. Excluded if serum vit D level was not recorded.	Age, sex, BMI, HPN indication, comorbidities that affect vit D, medications was taken from medical records. All received IV MVI containing 200UI of vit D. Oral supplementation of 50000 IU was prescribed for patients identified to have a vit D level <20ng/mL.	20 Sufficient 24 Insufficient 35 Deficient 35 were prescribed 50000IU weekly 44 were prescribed 50000IU twice weekly 24 were prescribed 50000IU thrice weekly Absence of jejunum was associated with 5 fold increased in likelihood of deficiency.	Only a small amount of HPN patients had sufficient levels. HPN patients should be routinely screened for Vit D status.	Retrospective study, unable to assess how patients were taking oral supplements. HPN macronutrient content was not included in this study. It was assumed that macronutrients such as lipids would not affect metabolism of oral vitamin D supplementation. Only 79

			Routine assessment of serum vit d has become standard of practice.			of 467 patients on HPN were included due to vit d level.
Pittas, Anastassios G. et al. "Role of Vitamin D In Adults Requiring Nutrition Support". Journal of Parenteral And Enteral Nutrition, vol 34, no. 1, 2009, pp. 70-78. Wiley, doi:10.1177/0148607109349061. Grade I	Reviews methods for assessing vitamin D status and strategies to restore vitamin D status in patients on EN or PN who are at high risk for low vitamin D levels.					
Fan, S., Ni, X., Wang, J., Zhang, Y., Tao, S., Kong, W., Li, Y. and Li, J. (2016). High Prevalence of Suboptimal Vitamin D Status and Bone Loss in Adult Short Bowel Syndrome Even After Weaning Off Parenteral Nutrition. Nutrition in Clinical Practice, 32(2), pp.258-265. Grade I	Limited data on short bowel without parenteral dependence. Investigate incidence of suboptimal vitamin d status and bone loss in adult short bowel syndrome after weaning off parenteral nutrition.	Prospective study of 60 adult patients with SBS.	Serum vit D was measured. BMD was measured. Medical records and various labs were collected	Suboptimal vitamin D levels were found in all individuals studied. Low vitamin d levels are associated with BMD. Even with vitamin D replacement is was difficult to achieve satisfactory status.	Importance in surveillance of vit D levels and BMD and considerations of alternative methods following weaning parenteral nutrition.	1)single center study 2)only 60 patients with SBS

Napartivaumnuay, Navaporn, and Leah Gramlich. "The Prevalence of Vitamin D Insufficiency and Deficiency and Their Relationship With Bone Mineral Density And Fracture Risk In Adults Receiving Long-Term Home Parenteral Nutrition". Nutrients, vol 9, no. 5, 2017, p. 481. MDPI AG, doi:10.3390/nu9050481. Grade I	Retrospective, observational Determine prevalence of vitamin D insufficiency/deficiency and bone mineral density and 10-year fx risk in adults on long term HPN.	Northern Alberta, Canada on HPN. All patients received IV MVI routinely containing 200IU of vitamin D3. Adult patients on HPN >6 months. Those with malignancy or that did not have a vit D level or BMD were excluded.	Eligible patients grouped according to vit D levels, sufficient, insufficient, deficient. Presence of bone mineral disease and degree.	62 of 186 patients were included. Mean age 53.8 Most common cause for HPN was short bowel syndrome. Mean vit d level was 25.6ng/mL. 15 were sufficient 31 insufficient 16 deficient. 64.5% have abnormal BMD. 50% had mod-high fx risk.	There was found to be suboptimal levels of vitamin D commonly in home HPN long term patients.	Small study Retrospective
Intestinal Failure						
Grenade, N., Kosar, C., Steinberg, K., Avitzur, Y., Wales, P. and Courtney-Martin, G. (2016). Use of a Loading Dose of Vitamin D for Treatment of Vitamin D Deficiency in Patients with Intestinal Failure. Journal of Parenteral and Enteral Nutrition, 41(3), pp.512-516. Grade I	To determine a loading dose in vitamin d deficient patients with intestine failure	Review of patient cases in which loading dose was trailed in pediatric patients that had intestinal failure	Review of patient cases in which loading dose was trailed in pediatric patients that had intestinal failure	Treatment with a dose of vitamin D one time per week, has been shown to restore serum levels of 25-OH-D to normal levels in children with short bowel syndrome.	D3 cholecalciferol exhibits an effect treatment for children with intestinal failure. 20000-40000 IU of vitamin D once per week and a daily dose of 4000-6000 IU/d	Limited studies using loading dose.

					on the remaining 6 days.	
Ellegård, L., Kurlberg, G. and Bosaeus, I. (2013). High prevalence of vitamin D deficiency and osteoporosis in out-patients with intestinal failure. Clinical Nutrition, 32(6), pp.983-987. Grade I	To determine prevalence of vitamin D deficiency and osteoporosis in those with intestinal failure.	106 patients who were seen 1 or more times by an outpatient surgical clinic for intestinal failure with the department of surgery in sahlgrenska university hospital were reviewed in Gothenburg, Sweden	Serum vitamin D levels were taken. Severe < 25 nmol/l Deficiency <50nmol/l Marginal vitamin D <75 Optimal 75-150 Retinol was looked at in 48 patients, a-tocpherol in 47 patients, vitamin A and E were defined as <1 and <14nmol Bone density was assessed by DXA in78 patients Osteoporosis was defined as spinal or bone density score T score below -2.5 SD and osteopenia	45 patients were only taking a multivitamin which included 5 ug of vitamin D. 29 were on PN supplementation, 29 were on ca and vit D supplementation, 3 were on indv doses of vitamin d. The 45 on an MVI had lower vit d levels compared to the 61 on supplementation. 67% of patients had a serum level <50, 25% were severely deficient, 12% had optimal levels. No significant differences with or without PN.	No correlation was found between vitamin D levels and bone density in lumbar or femoral regions.	Latitude was not assessed

			was defined as a t score between -1 and-2.5. Height and weight were also measured.	12% that had a DXA scan were normal, 44% were osteopenia and 44% osteoporotic.		
Margulies, S., Kurian, D., Elliott, M. and Han, Z. (2015). Vitamin D deficiency in patients with intestinal malabsorption syndromes - think in and outside the gut. Journal of Digestive Diseases, 16(11), pp.617-633.	Review	Review	Review	Review	•High instance of vitamin D deficiencies in patients with intestinal malabsorption •No strong relationship between intestinal vitamin d absorption and deficiency •Insufficient sunlight exposure is a significant factor for vitamin d deficiency in patients with intestinal malabsorption syndromes. •Inflammation and hyperparathyroidism are	

					important in vit d deficiencies as a cause when an intestinal malabsorption syndrome is present. •IBD including crohns and UC can be caused by genetic and environmental factors. Vit d def in presence of IBD. •Reduced vitamin d absorption ability in patients with intestinal malabsorption •Vitamin d supplementation for cyctic fibrosis •Celiac disease and vitamin d supplementation •Vit d supplementation for patients with IBD	

Inflammatory Bowel Disease						
Sharifi, A., Nedjat, S., Vahedi, H., Veghari, G. and Hosseinzadeh-Attar, M. (2018). Vitamin D Status and Its Relation to Inflammatory Markers in Patients with Mild to Moderate Ulcerative Colitis. Middle East Journal of Digestive Diseases, 10(2), pp.84-89. Grade I	to assess the vitamin D status and its associations with erythrocyte sedimentation rate (ESR) and high sensitivity c-reactive protein as inflammatory markers in UC patients.	analytical cross-sectional study, 90 patients with mild-mod UC were assessed.	25OHD, parathyroid hormone, ESR and hs-CRP were measured. 3-day dietary recall, stats by STATA.	mean 25OHD was 33.1. 38.9% of patients were vit d def or insufficient. No sig correlation between 25OHD, hs-crp, BMI and disease duration. No differences in serum vit D between men and women. Mean daily intakes from diet and calcium were 189.5IU and 569.5mg	mean 25OHD was 33.1. 38.9% of patients were vit D def or insufficient. No sig correlation between 25OHD, hs-crp, BMI and disease duration. No differences in serum vit D between men and women. Mean daily intakes from diet and calcium were 189.5IU and 569.5mg	No control group. 39 patients declined to participate. Only patients with mild-mod UC were assessed.
Vernia, P., Burrelli Scotti, G., Dei Giudici, A., Chiappini, A., Cannizzaro, S., Afferri, M. and de Carolis, A. (2018). Inadequate sunlight exposure in patients with inflammatory bowel disease. Journal of Digestive Diseases, 19(1), pp.8-14. Grade I	Evaluate sunlight exposure in patients with IBD-inflammatory bowel disease in Italy.	Case controlled study, 292 patients with IBD. 132 had Crohn's, 160 with UC. 80 diseased patients and 540 healthy controls.	Validated questionnaire to evaluate sunlight exposure. Data was then compared with age and gender.	78 or 292 patients with IBD had low sun exposure. 169 had moderate sun exposure. 45 had high exposure. 132 with Crohn's disease were more likely to have abnormal sun exposure than those with	Patients with inflammatory disease had significantly less sunlight exposure than controls in Italy. Patients with IBD may benefit from increase sunlight exposure, it areas that are more at risk for	One location

				UC. The control group had more sun exposure.	less sun. Vit D levels when not taking oral supplements did not seem to correlate significantly with sun exposure in IBD.	
Lund-Nielsen, J., Vedel-Krogh, S., Kobylecki, C., Brynskov, J., Afzal, S. and Nordestgaard, B. (2018). Vitamin D and Inflammatory Bowel Disease: Mendelian Randomization Analyses in the Copenhagen Studies and UK Biobank. The Journal of Clinical Endocrinology & Metabolism, 103(9), pp.3267-3277. Grade I	Serum levels of 25(OH)D may be associated with risk of Crohn's disease and ulcerative colitis.	Mendelian randomization study, 120,013 subjects from Copenhagen City Heart Study, Copenhagen General Population Study, Copenhagen patients with IBD.	35,558 has serum vitamin D levels and 115,110 were genotyped. 653 cases were identified for Crohn's (58 vit d available) and 1265 cases for ulcerative colitis (113 vit D available). Hazard ratios for higher plasma vitamin d levels were examined.	Hazard ratios for 10 nmol/L higher 25OHD were 1.04 for Crohn's and 1.13 for UC. Combined allele score for 25OHD was associated with an increase in plasma 25OHD by 1.4 nmol/L	A major role of vitamin D levels and IBD was not shown.	Genetic pleiotropy and linkage diequilibrium
Zammit, S. (2018). Vitamin D deficiency in a European inflammatory bowel disease inception cohort: an Epi- IBD study. European Journal of Gastroenterology & Hepatology, 2018, pp.1-7.	Determine relationship of demographics, severity, phenotype and QOL, treatments received in	238 patients were included with IBD from 2010-2011. Patients had vitamin D levels available and	IBD was measured using the Harvey Bradshaw Index for CD	Of 238 patients a total of 188 patients were from western European countries. The remainder were	Vitamin D levels at dx can indicate presence of more severe IBD. Smoking was associated	Factors that influence vitamin D in IBD

Grade I	patients with IBD with low serum vitamin D levels	had serum vitamin D measured at follow up appointments. All were part of Epi- IBD cohort.	and SCCAI for UC. QOL was measured using IBD short questionnaire. Demographics, and treatments were recorded. Vitamin D was measured and deficient was classified<50nmol/l Insufficient 50-75nmol/l Normal </= 75nmol/l Other factors such as sex, phenotypes, disease activity, medications used, smoking and surgery were also looked at.	from eastern European countries. 16 of the patients underwent surgery over a 5 year period. Female patients had higher vitamin d levels overall at dx. 79% of participants were insufficient or deficient at diagnosis and no difference in type of IBD. A positive correlation was found between serum vitamin d levels and time since initial dx of IBD and being on appropriate medications. Only 2 patients were on vitamin d supplementation the first year of dx.	with lower serum vitamin d levels. Vitamin D and QOL had a known association. Serum vitamin d and wellbeing were associated.	

Han, Y., Yoon, H., Lim, S., Sung, M., Shin, C., Park, Y., Kim, N., Lee, D. and Kim, J. (2017). Risk Factors for Vitamin D, Zinc, and Selenium Deficiencies in Korean Patients with Inflammatory Bowel Disease. Gut and Liver, 11(3), pp.363-369. Grade I	Micronutrient deficiency as well as risk factors for deficiency in IBD patients in Korea.	83 IBD patients in Korea were recruited from 2013 to 2015 at Seoul National University Bundang Hospital who had blood levels for vitamin d, zinc and selenium.	Serum 25OHD, zinc and selenium were examined. Vitamin D was also looked at in IBD vs healthy patients, in age and sex-controlled groups.	74/83 had suboptimal vitamin D levels. Those with IBD had significantly reduced levels compared to healthy subjects. 39% had lower serum zinc and 30.9% had lower selenium levels. Female and Crohn's disease were more likely to have vitamin d deficiency. Those <40 years of age were more likely to have a zinc deficiency. Female and lower serum albumin were risk factors in selenium deficiency.	Monitoring of micronutrients in Koreans with IBD is suggested.	Disease activity was not measured due to retrospective study. Dietary intake was also not monitored.
Frigstad, S., Høivik, M., Jahnsen, J., Dahl, S., Cvancarova, M., Grimstad, T., Berset, I., Huppertz-Hauss, G.,	Determine the prevalence of vitamin D deficiency and	IBD patients were recruited from 9 local hospitals in	Data from clinical and epidemiologica l were	200/408 49% of subjects had a serum vitamin d level <	In CD and UC vitamin d def was common (higher in CD)	Did not test sunlight exposure.

Hovde, Ø., Torp, R., Bernklev, T., Moum, B. and Jelsness-Jørgensen, L. (2016). Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population. Scandinavian Journal of Gastroenterology, 52(1), pp.100-106. Grade I	variables associated with this deficiency in IBD outpatients.	Norway. And enrolled in an observational, multi center study from March 2013 to April 2014.	collected from medical records and interviewing of subjects. Serum vit D was performed in a laboratory.	50nmol/L. 53% with CD, 44% with UC. In CD disease activity measured as the HBI was inversely associated with vit d def. No association was seen in UC using the SCCAI scores. In CD there was an association with vit D def and relapses in the previous year.	and associated with disease activity, relapses and higher inflammatory activity.	
Caviezel, D., Maissen, S., Niess, J., Kiss, C. and Hruz, P. (2017). High Prevalence of Vitamin D Deficiency among Patients with Inflammatory Bowel Disease. Inflammatory Intestinal Diseases, 2(4), pp.200-210. Grade I	Vitamin D levels were compared between IBD patients and IBS patients.	Cross sectional study 181 patients, 156 with IBD and 25 with IBS	Disease activity, inflammatory markers, physical activity and season were collected.	58 CD patients and 25 UC patients had a vitamin D level < 50nmol/L. CD had significantly lower levels than IBS patients. This was not found in UC patients. Seasonal variation was also seen in CD patients. Lower	Vitamin D deficiency was common in all IBD, but higher in CD patients.	Small number of IBS patients

				values in the spring than summer.		
Tan, B., Li, P., Lv, H., Yang, H., Li, Y., Li, J., Wang, O. and Qian, J. (2018). Treatment of vitamin D deficiency in Chinese inflammatory bowel disease patients: A prospective, randomized, open-label, pilot study. Journal of Digestive Diseases, 19(4), pp.215-224. Grade I	Evaluate vitamin D supplements in Chinese inflammatory bowel disease UC and CD that were experiencing insufficiency or deficiency.	Prospective, parallel-controlled, open-label, pilot randomized clinical study. UC and CD patients in IBD clinic of Peking Union Medical College Hospital between Dec 2010 and Feb 2014. Inclusion criteria Adult >18years with UC/CD Vitamin D insufficiency or deficiency by 12-month f/u.	Patients were randomly assigned into 3 groups. One group received vit d3, 150000IU one per 3 months and 200mg elemental calcium. 2nd group 200mg elemental calcium 3x per day. 3rd group control group. Improvement in 25OHD was assessed as well as bone density and disease activity.	65 UC and 59 CD patients completed the study. The pre and post treatment of group 1 had higher levels of 25oHD than 2 or 3. No difference in bone density or disease activity.	Vitamin D supplementation is required to treat insufficiency and deficiency in UC and CD patients regardless of disease activity.	Participants and investigators were not blinded. Most of the Crohn's disease patients were currently in remission or mild disease.
Schäffler, H., Schmidt, M., Huth, A., Reiner, J., Glass, Ä. and Lamprecht, G. (2018). Clinical factors are associated with vitamin D levels in IBD patients: A retrospective	Determine if there is a correlation between vitamin d deficiency and clinical parameters in IBD.	Retrospective study of patients with IBD. Outpatient clinic in Rostock, Germany	Patients were divided into 2 groups, one with vitamin D supplements and one without. All	208 IBD patients were evaluated. 123 CD, 85 UC. Treatment with azathioprine did not seem to affect vitamin D	Vitamin D deficiency is common in patients with IBD and may require close	Did not test sunlight exposure in these patients.

analysis. Journal of Digestive Diseases, 19(1), pp.24-32. Grade I		enrolled patients with UC/CD from Jan 2011 to Sept 2014 and were retrospectively analyzed.	had serum vit D levels and disease activity evaluated. Severe deficiency <27.5 nmol/L, deficiency <50nmol/L, insufficiency <75nmol/L, normal >75nmol/L.	levels or disease activity. Significantly lower vitamin D levels were found in CD patients or if more of the bowel had been resected.	monitoring for deficiency.	
Venkata, K., Arora, S., Xie, F. and Malik, T. (2017). Impact of vitamin D on the hospitalization rate of Crohn's disease patients seen at a tertiary care center. World Journal of Gastroenterology, 23(14), p.2539. Grade I	Examine the relationship between vitamin d and hospitalization rate in Crohn's disease.	Retrospective cohort study in adult patients with CD for at least one year.	Serum vitamin D levels were assessed and divided into low mean vitamin d level <30 ng/ml vs normal 30-100ng/ml. Generalized Poisson Regression Models were used, and incidence rate ratios were used for CD that had been hospitalized. 880 CD patients were	CD with a lower mean vitamin D level were 2x more likely to be hospitalized compared to those with a normal vitamin D level. Higher vitamin d levels were associated with 3% lower likely hood of admission.	Normal vitamin D levels may be beneficial in CD clinical course.	Small number of hospitalized patients were looked at. Retrospective study and EMR use.

			looked at. 196 had vitamin D levels and were included.			
Sharifi, Amrollah et al. "Vitamin D Status and Its Relation to Inflammatory Markers In Patients With Mild To Moderate Ulcerative Colitis". Middle East Journal of Digestive Diseases, vol 10, no. 2, 2018, pp. 84-89. International Society for Phytocosmetic Sciences, doi:10.15171/mejdd.2018.95. Grade I	Cross-sectional study Assess vitamin D status in Iranian patients with UC and its correlation with ESR, hs-CRP.	129 Tehran inhabitants, ages 18-50 with mild to moderate UC. Ultimately 90 participated.	Blood samples of 25 (OH)D3, hsCrp and ESR were measured. Demographic data was collected was collected by interviewing participants.	Avg serum vit D was 33.1 +/- 8.3 ng/mL. 37.3% of men and 41% of women were deficient or insufficient. No sig correlation was found between vitamin D and hs-CSR, ESR.	Those with mild-mod UC that had vit D insufficient or deficient were not corollate with hs-CRP, ESR. More studies are needed.	No control group. Of 129 eligible participants only 90 participated. Only patients with mild-mod UC and between the ages of 18-50 were included.
Ulitsky, Alex et al. "Vitamin D Deficiency in Patients with Inflammatory Bowel Disease". Journal of Parenteral and Enteral Nutrition, vol 35, no. 3, 2011, pp. 308-316. Wiley, doi:10.1177/0148607110381267. Grade I	Examine the potential association of vitamin D deficiency with increased inflammatory bowel disease and the decline in quality of life.	Retrospective, observational study Patients being followed in the Medical College of Wisconsin's IBD Center.	25(OH)D level Demographic data, disease location and medication use was obtained. IBD questionnaire to determine quality of life.	504 IBD patients, 403 Crohn's, 101 UC. 49.8% were deficient and 10.9% severely deficient. Deficiency was associated with lower quality of life score.	Vitamin D deficiency is common in patients with IBD and lower quality of life.	Retrospective
Del Pinto, Rita et al. "Association Between Inflammatory Bowel Disease and Vitamin D Deficiency".	Look at the association between IBD and Vitamin D	Meta-analysis and systemic review.	Electronic databases were examined from by 2	IBD patients were 64% higher chance of being Vitamin	IBD is associated with having an increased chance of	Observational

Inflammatory Bowel Diseases, vol 21, no. 11, 2015, pp. 2708-2717. Oxford University Press (OUP), doi:10.1097/mib.0000000000000546.			different authors for presence of Vitamin D deficiency and IBD and a control group without IBD. 14 studies were identified. 938 control and 953 control.	D deficient, compared to control group. Latitude did not seem to impact results.	Vitamin D deficiency.	
Liver Disease						
Ahmed, Furqaan. "Prevalence of Vitamin D Deficiency Among Non-Cirrhotic Pakistani Patients with Chronic Viral Hepatitis And Non-Alcoholic Fatty Liver Disease". Journal of Liver: Disease & Transplantation, vol 04, no. 02, 2015. OMICS Publishing Group, doi:10.4172/2325-9612.1000129. Grade I	Determine prevalence of vitamin D deficiency in patients with chronic liver disease and its relationship to severity of liver dysfunction.	118 patients with chronic liver disease at the Hepatology Clinic at the University of Tennessee Health Science Center. 59 males and 59 females.	Vitamin D status and clinical profile was examined. Analysis was preformed to determine if age, gender, race, BMI, DM or severity of disease planned a role in vitamin D deficiency.	Vitamin D deficiency was observed in 109 out of 118 patients.	92% of chronic liver disease patients experience vitamin d deficiency.	PTH was not measured and could not explain the interaction between PTH and vitamin d calcium levels in liver disease.
Barchetta, Ilaria et al. "Strong Association Between Non-Alcoholic Fatty Liver Disease (NAFLD) And Low 25(OH) Vitamin D Levels in An Adult	Test a hypothesis that there was an association between	262 subjects from the Diabetes and Hepatology clinic of	NAFLD was dx by ultrasound. Serum vitamin D measured.	Subjects with NAFLD were found to have lower levels of	Lower serum vitamin was associated with NAFLD	Ultra sound is not the gold standard to detect liver disease

Population with Normal Serum Liver Enzymes". BMC Medicine, vol 9, no. 1, 2011. Springer Nature, doi:10.1186/1741-7015-9-85. Grade II	hypovitaminosis D and the NAFLD.	Sapienza University of Rome.		vitamin D than those without.		although practical. Cross-sectional design due to no established causality nexus. Less common liver diseases causes could not be ruled out.
Eliades, M. et al. "Meta-Analysis: Vitamin D and Non-Alcoholic Fatty Liver Disease". Alimentary Pharmacology & Therapeutics, vol 38, no. 3, 2013, pp. 246-254. Wiley, doi:10.1111/apt.12377. Grade I	Study the association between vitamin D levels and NAFLD	Studies were compared from PubMed and EMBASE regarding vitamin D status and NFLD	17 cross sectional and case-controlled studies were evaluated	Deficiency of vitamin D were 1.26 times more likely in those with NAFLD	NAFLD have decreased serum vitamin D levels determining as association.	Causal role could not be established and would require further studies.
Yang, et al. "The Value of Severe Vitamin D Deficiency in Predicting the Mortality Risk of Patients with Liver Cirrhosis: A Meta-Analysis". Clinics and Research in Hepatology and Gastroenterology, 2019. Elsevier BV, doi: 10.1016/j.clinre.2019.03.001. Grade II	Look at the relationship between severe Vitamin D deficiency and mortality of liver cirrhosis patients.	Meta- analysis of observational studies.	8 studies from March 2013 to Jan 2019 were included	Severe vitamin D deficiency was associated with a higher risk of mortality in cirrhosis liver disease patients.	Vitamin D level may be a new level to use to look at prognosis in liver cirrhosis patients. Vitamin D supplementation was strongly suggested in these patients.	All studies were conducted in Europe. May not reflect the entire world. Larger populations could be looked at. Small sample size.

Wang, Ningjian. "Vitamin D and Nonalcoholic Fatty Liver Disease: Bi-Directional Mendelian Randomization Analysis". *Ebio medicine*, vol 28, 2018, pp. 187-193., doi: 10.1016/j.ebiom.2017.12.027. Accessed 18 July 2019. Grade I	Look at the relationship between Vitamin D and NAFLD	9182 participants were polled in a study in Eastern China in 2014 to 2016.	Genetic risk scores were calculated for vitamin D levels and NAFLD. Liver steatosis was looked at by ultrasound.	Increased genetic risk scores were associated with Vitamin D levels but not with NAFLD.	No causal relationship between NAFLD and Vitamin D status	Study was conducted in China, not represented of the entire world. Vitamin D was only measured once.

Results Review

The most common areas involving gastrointestinal disease and Vitamin D were divided into subgroups to understand further the prevalence of Vitamin D deficiency in that particular disease state.

Parenteral Nutrition

Because the majority of patients requiring parenteral nutrition are not able to meet their estimated nutritional needs orally due to obstruction or absorption issues, the absorption of Vitamin D and calcium can also be impacted. While sunlight exposure can synthesize Vitamin D, dietary intake of Vitamin D sources also plays a role and requires parts of the small bowel, liver, and pancreas for Vitamin D absorption. Vitamin D insufficiency in these patients increases the risk for metabolic bone disease and can cause other complications such as falls and fractures requiring hospitalization (Deluca, 2009).

In reviewing studies involving prevalence of low Vitamin D status and individuals requiring parenteral nutrition, the majority studied were receiving home parenteral nutrition (PN) due to their stability on PN versus hospitalized individuals (Bharadawaj, et al., 2012; Thomson, et al., 2011; Deluca, 2009). Reasons found for requiring parenteral nutrition including gastrointestinal dysmotility, short bowel syndrome, and malabsorption. A high prevalence of Vitamin D deficiency and insufficiency was demonstrated in home parenteral nutrition patients (Thomson et al., 2011). Lab values such as 25(OH)D, phosphorus, magnesium and ionized calcium were analyzed (Thomson et al., 2011). Dietary recall was also examined in multiple studies for Vitamin D content and its role in Vitamin D status. The incidence of less than optimal Vitamin D status and bone loss in adults with short bowel syndrome after weaning off total parenteral nutrition was also examined (Fan et al, 2016).

Supplementation of Vitamin D in home PN patients is common but limited. It was found that home parenteral nutrition patients were receiving an IV multivitamin in their parenteral nutrition formulation that included 200- 400IU of Vitamin D (Thomson et al., 2011; Bharadawaj et al., 2012; Deluca,2009; Napartivaumnuay et al., 2017). Oral supplementation of 50000 IU was prescribed for patients identified to have a 25(OH)D level < 20ng/mL identifying deficiency (Bharadawaj et al., 2012).

Outcomes in parenteral nutrition patients demonstrated chronic insufficiency, with only small amounts of home parenteral nutrition patients having sufficient levels (Bharadawaj et al., 2012). It was thought that limited exposure to sunlight due to chronic conditions, as well as gastrointestinal disorders impairing Vitamin d absorption, played a role (Thomson et al., 2011). Deficiency was common even in PN patients on oral supplementation, and even at higher replacement doses it was hard to achieve satisfactory status (Fan et al., 2016). Patients on home PN were also at increased risk of metabolic bone disease as it was found that low vitamin D levels impacted low bone mineral density as well (Fan, et al., 2016; Deluca, 2009).

Recommendations in patients dependent on parenteral nutrition, included routine screening for Vitamin D status and vitamin D levels are kept within normal range as able (Bharadawaj et al., 2012; Deluca, 2009). Supplementation of Vitamin D by mouth, as well as through parenteral nutrition multivitamin were recommended in addition to routine screening. (Thomson et al., 2011). Other recommendations included screening for bone mineral density routinely and considering alternative methods of supplementation when weaning from parenteral nutrition (Fan, et al., 2016). Further research on the use of UV exposure therapy may be beneficial as IV Vitamin D is currently not available in the United States (Deluca, 2009).

Hepatic Disease

Patients that experience liver failure or diseases affecting the liver are at risk for Vitamin D deficiency, due to the liver's impaired ability to properly synthesize vitamin D (Nair, 2012). A study involving 118 liver disease patients found that 92.4% of them has some degree of Vitamin D deficiency (Nair,2012; Ahmend et al, 2015). The degree of deficiency seemed to be related to the severity of liver disease and impairment, but deficiency was also observed in patients without liver failure (Nair, 2012). Patients who have undergone a liver transplant and

Liver transplant patients who experience Vitamin D deficiency could experience an accelerated loss of bone due to increased risk (Nair,2012). Side effects of interferon therapy, commonly taken in transplant patients, such as achy muscles, could be exacerbated by low Vitamin D levels as well (Nair, 2012).

Vitamin D status and nonalcoholic fatty liver disease (NAFLD) had a strong association. Lower serum Vitamin D levels were observed in subjects with NAFLD than those without (Barchetta et al., 2011). It was concluded subjects with NAFLD were 1.26 times more likely to experience Vitamin D deficiency (Eliades et al., 2013). Severe Vitamin D deficiency was associated with a higher risk of mortality in cirrhosis liver disease patients (Yang, 2019). Emerging research suggest Vitamin D level may be a new level to look at potential prognosis in liver cirrhosis patients (Yang, 2019).

Awareness of Vitamin D deficiency and liver disease can help encourage monitoring of Vitamin D status and initiating supplementation (Nair, 2012). Vitamin D supplementation may also be beneficial for patients with liver disease in the progression of disease and treatment response (Keane, 2018). A clinical trial was conducted looking at patients with non-alcoholic fatty liver disease. It was noted that the supplementation of Vitamin D helped to reduce fat infiltration in the liver (Ifigenia, et al, 2016). Initially, the liver was studied due to the presence of

Vitamin D receptors within the liver and found that the most severe cases of Vitamin D deficiency, was correlated with severe cases of non-alcoholic fatty liver disease (Ifigenia, et al, 2016). It was concluded that Vitamin D supplementation improved hepatic steatosis after only four weeks (Ifigenia, et al, 2016).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) typically refers to Crohn's disease and ulcerative colitis. Vitamin D status can be an issue in those affected by this disease as they can experience absorption issues or surgical resections of the intestine. Vitamin D plays a role in maintaining the integrity of the gastrointestinal barrier, immune response and a role in surveying the gut microbiota, which can play a role in the disease progression and patients' symptoms (Fletcher et al, 2019).

Studies involving IBD and Vitamin D status looked at several areas to see if a correlation was present. Areas explored IBD and inflammatory state of the bowel, the association of Vitamin D and erythrocyte sedimentations rate (ESR) as well as high sensitivity C- reactive protein measurements in ulcerative colitis patients (Sharifi et al., 2018). No significant correlation was found between 25(OH)D levels, high sensitivity C-reactive protein, BMI or the duration of disease (Sharifi et al, 2018). No difference in serum Vitamin D levels was observed among both sexes. It was noted 38.9% of patients were insufficient or deficient in Vitamin D. The risk of IBD and serum levels of 25(OH)D was also examined in both Crohn's and ulcerative colitis patients. No major role of Vitamin D levels and inflammatory bowel disease was demonstrated (Lund-Nielsen et al., 2018). A positive correlation was also seen between serum Vitamin D levels and the time between initial diagnosis and being on appropriate interventions (Zammit, et al., 2018). Vitamin D status and quality of life in these patients were also

associated. Obtaining Vitamin D levels upon diagnosis is helpful in it may be used to indicate the severity of the disease (Zammit et al., 2018). Those that had inflammatory bowel disease were compared to healthy people of the same age and found to have significantly reduced levels compared to healthy subjects. Those that were female and had Crohn's disease were more likely to be Vitamin D deficient (Han et al., 2017).

Studies compared if Crohn's had the same prevalence for Vitamin D insufficiency as ulcerative colitis. It was found that 49% of subjects who had serum Vitamin D levels < 50nmoll/L 53% had Crohn's disease and 44% had ulcerative colitis. There was an association between Crohn's disease relapses within the last year and Vitamin D deficiency. Vitamin D deficiency was common in all inflammatory bowel disease patients but higher in those with Crohn's (Frigstad et al., 2016). Another cross-sectional study compared Vitamin D levels and inflammatory bowel disease patients and irritable bowel disease patients. Fifty-eight Crohn disease patients and 25 ulcerative colitis patients had a Vitamin D level less than 50 nmol/L, indicating insufficiency or deficiency. Patients with Crohn's disease had significantly lower levels of Vitamin D than those with irritable bowel disease; this relationship was not found in those with ulcerative colitis (Caviezel et al., 2017). While Vitamin D deficiency is common in inflammatory bowel disease patients, it was more common specifically in Crohn's disease patients than ulcerative colitis patients (Caviezel et al., 2017). IBD patients were 64% higher chance of being Vitamin D deficient, compared to a control group (Del Pinto, 2015). Findings suggested latitude did not seem to impact results (Del Pinto, 2015).

Supplementation was also trialed in patients with inflammatory bowel disease (IBD). A prospective, pilot randomized controlled trial to evaluate Vitamin D supplementation in patients with inflammatory bowel disease that were deficient or insufficient in Vitamin D was conducted. Three groups were formed, one received Vitamin D supplement, one received elemental

calcium, and one group received nothing. The group that received the Vitamin D supplementation had higher levels of 25OHD than the other two groups. It was determined that Vitamin D supplementation is necessary in this population (Tan et al., 2018).

Vitamin D status may also play a role in hospitalizations in patients with IBD. A retrospective study to examine the relationship between Vitamin D and hospitalization rate in patients with Crohn's disease. It was found that patients with Crohn's disease and low Vitamin D were two times more likely to be hospitalized than those with normal Vitamin D levels. Higher Vitamin D levels were associated with 3% lower likelihood of hospital readmission. It was found that adequate Vitamin D status may be beneficial in Crohn's patients' clinical course (Venkata et al., 2017).

Intestinal Failure

A review examined the loading dose Vitamin D deficient patients with intestinal failure. It was found that Vitamin D3 cholecalciferol was an effective treatment in patients with intestinal failure. It was effective between 20000-40000IU one time per week or 4,000-6,000 IU/day on the other 6 days of the week (Grenade et al., 2016). Those with intestinal failure may also be relying on parenteral nutrition or a combination of parenteral and oral nutrition. The relationship with intestinal failure patients, Vitamin D status and bone density in lumbar and femoral regions were examined to determine if they were at higher risk of osteoporosis. It was found there was not a correlation between Vitamin D levels and bone density in these regions (Ellegard et al., 2013). Subjects that were only taking a multivitamin that contained Vitamin D had lower Vitamin D levels compared to those on Vitamin D and calcium supplementation. It was thought that inadequate sunlight exposure may plan a stronger role in these patients, rather than the inability of the intestine to absorb Vitamin D (Margulies et al., 2015).

Treatment recommendations

Different Vitamin D treatment regimens were evaluated and their response to serum vitamin D levels in a retrospective study. Subjects were given doses of cholecalciferol ranging from 600IU to 1100IU and demonstrated similar changes in serum Vitamin D levels of 8-9.1 mg/mL. A larger increase in serum Vitamin D levels of 12.7ng/mL was seen with a dose of 2700IU. A mean dose of ergocalciferol, 11000IU demonstrated an increase of 19.9ng/mL in serum Vitamin D levels. Supplementing with lower Vitamin D doses demonstrated a similar effect on serum Vitamin D change. Higher doses of supplements can produce higher levels of Vitamin D, but the relationship was not linear (Atterrado et al., 2015).

Limitations:

While this is an important subject, clinicians can be biased on personal practices. As far as research limitations, many studies regarding this subject included pediatrics, especially in parenteral nutrition patients and therefore were excluded. Areas such as inflammatory bowel disease had been explored in depth more recently, while intestinal failure and hepatic disease did not have as much literature.

Conclusion:

Overall, while there were limited studies on adults on parenteral nutrition and Vitamin D status, it was found only small amounts of individuals on parenteral nutrition had satisfactory Vitamin D status. These individuals also had limited absorption of Vitamin D orally due to bowel malabsorption but if able to take medications orally, it is recommended to trial oral Vitamin D replacement. Limited Vitamin D is provided within the multivitamin within the parenteral

nutrition formulation, only approximately 400IU. Close monitoring and replacement as indicated is recommended in parenteral nutrition dependent individuals.

Very limited research was found regarding intestinal failure and Vitamin D status. Individuals that were only receiving Vitamin D supplement provided in parenteral nutrition multivitamin were at higher risk of insufficiency than those on oral replacement Vitamin D as well. Hepatic diseases were also limited in research with Vitamin D status. Findings of these limited studies suggested a relationship with 92% of chronic liver disease patients experiencing Vitamin D deficiency and lower serum vitamin D levels in those with nonalcoholic fatty liver disease.

Inflammatory bowel disease and Vitamin D status had the most studies that were conducted recently. This may be because of new research connecting Vitamin D and the gastro-intestinal barrier integrity and immune response. The relationship between inflammatory bowel disease and Vitamin D deficiency is still not fully understood and it's unclear if the deficiency came before the disease or vice versa. Vitamin D status and IBD individuals did not seem to vary depending on sex, age BMI, or disease duration. Vitamin D deficiency was common in IBD individuals, more common in Crohn's individuals than ulcerative colitis. There may be an association with disease activity, relapse and inflammatory activity. It was found Crohn's patients were less likely to get sun exposure than UC patients and they were also more likely to be deficient than UC patients. Lower Vitamin D levels may indicate severe IBD, quality of life and Vitamin D status were associated, and smoking was associated with lower vitamin D levels. Supplementation was recommended regardless of disease activity as well as routine screening. Monitoring of all micronutrients in IBD patients was recommended as well due to impaired gut function. Further research is needed to determine if supplementing Vitamin D improves inflammation and severity of disease in IBD patients.

Vitamin D status should be obtained on the following types of patients Crohn's disease, ulcerative colitis disease, hepatic disease, short gut syndrome, and other bowel resection surgeries as well as those on parenteral nutrition with malabsorption disorders, to determine if deficiency or insufficiency is present.

References

1. Adorini, Luciano et al. "Vitamin D Receptor Agonists, Cancer and The Immune System: An Intricate Relationship". *Current Topics in Medicinal Chemistry*, vol 6, no. 12, 2006, pp. 1297-1301. Bentham Science Publishers Ltd., doi:10.2174/156802606777864890
2. Ahmed, Furqaan. "Prevalence of Vitamin D Deficiency Among Non-Cirrhotic Pakistani Patients with Chronic Viral Hepatitis and Non-Alcoholic Fatty Liver Disease". *Journal of Liver: Disease & Transplantation*, vol 04, no. 02, 2015. OMICS Publishing Group, doi:10.4172/2325-9612.1000129.
3. Armbrecht HJ et al. “Hormonal regulation of 25-hydroxyvitamin D3-1alpha-hydroxylase and 24-hydroxylase gene transcription in opossum kidney cells”. *Arch Biochem Biophys*. 2003; 409:298-304.
4. Aterrado, Sheryl et al. "Evaluating Vitamin D Repletion Regimens and Effects in Veteran Patients". *Annals of Pharmacotherapy*, vol 49, no. 9, 2015, pp. 969-977. SAGE Publications, doi:10.1177/1060028015591034.
5. Autier, Philippe. "Vitamin D Supplementation and Total Mortality". *Arch Intern Med*, vol 167, no. 16, 2007, pp. 1730-1737., Accessed 18 Jan 2019.
6. Battault, S. et al. "Vitamin D Metabolism, Functions and Needs: From Science to Health Claims". *European Journal of Nutrition*, vol 52, no. 2, 2012, pp. 429-441. Springer Nature, doi:10.1007/s00394-012-0430-5.
7. Barchetta, Ilaria et al. "Strong Association Between Non-Alcoholic Fatty Liver Disease (NAFLD) And Low 25(OH) Vitamin D Levels in An Adult Population with Normal Serum Liver Enzymes". *BMC Medicine*, vol 9, no. 1, 2011. Springer Nature, doi:10.1186/1741-7015-9-85.

8. Bharadwaj, Shishira et al. "Prevalence and Predictors of Vitamin D Deficiency and Response to Oral Supplementation in Patients Receiving Long-Term Home Parenteral Nutrition". *Nutrition in Clinical Practice*, vol 29, no. 5, 2014, pp. 681-685. Wiley, doi:10.1177/0884533614539178.
9. Bikle, Daniel D. "Vitamin D Insufficiency/Deficiency in Gastrointestinal Disorders". *Journal of Bone and Mineral Research*, vol 22, no. S2, 2007, pp. V50-V54. Wiley, doi:10.1359/jbmr.07s208.
10. Bikle, Daniel D. "Vitamin D Metabolism, Mechanism of Action, And Clinical Applications". *Chemistry & Biology*, vol 21, no. 3, 2014, pp. 319-329. Elsevier BV, doi: 10.1016/j.chembiol.2013.12.016.
11. Caviezel, Daniel et al. "High Prevalence of Vitamin D Deficiency Among Patients with Inflammatory Bowel Disease". *Inflammatory Intestinal Dise*ases, vol 2, no. 4, 2017, pp. 200-210. S. Karger AG, doi:10.1159/000489010.
12. Christakos, Sylvia et al. "Vitamin D Endocrine System and The Intestine". *Bonekey Reports*, vol 3, 2014. Portico, doi:10.1038/bonekey.2013.230.
13. Christakos, Sylvia et al. "Vitamin D: Metabolism, Molecular Mechanism of Action, And Pleiotropic Effects". *Physiological Reviews*, vol 96, no. 1, 2016, pp. 365-408. American Physiological Society, doi:10.1152/physrev.00014.2015.
14. Del Pinto, Rita et al. "Association Between Inflammatory Bowel Disease and Vitamin D Deficiency". *Inflammatory Bowel Diseases*, vol 21, no. 11, 2015, pp. 2708-2717. Oxford University Press (OUP), doi:10.1097/mib.0000000000000546.
15. DeLuca, Hector F. "Vitamin D and The Parenteral Nutrition Patient". *Gastroenterology*, vol 137, no. 5, 2009, pp. S79-S91. Elsevier BV, doi: 10.1053/j.gastro.2009.07.075.

16. Dusso, A. (2011). “Kidney disease and vitamin D levels: 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and VDR activation”. *Kidney International Supplements*, 1(4), pp.136-141. (Fix)
17. "EAL". Andeal.Org, 2019, https://www.andeal.org/content.cfm?content_id=11.
18. Eliades, M. et al. "Meta-Analysis: Vitamin D and Non-Alcoholic Fatty Liver Disease". *Alimentary Pharmacology & Therapeutics*, vol 38, no. 3, 2013, pp. 246-254. Wiley, doi:10.1111/apt.12377.
19. Ellegård, L. et al. "High Prevalence of Vitamin D Deficiency and Osteoporosis in Out-Patients with Intestinal Failure". *Clinical Nutrition*, vol 32, no. 6, 2013, pp. 983-987. Elsevier BV, doi: 10.1016/j.clnu.2013.02. 005..
20. Fan, Shengxian et al. "High Prevalence of Suboptimal Vitamin D Status and Bone Loss in Adult Short Bowel Syndrome Even After Weaning Off Parenteral Nutrition". *Nutrition in Clinical Practice*, vol 32, no. 2, 2016, pp. 258-265. Wiley, doi:10.1177/0884533616665784.
21. Fleet, James C., and Ryan D. Schoch. "Molecular Mechanisms for Regulation of Intestinal Calcium Absorption by Vitamin D and Other Factors". *Critical Reviews in Clinical Laboratory Sciences*, vol 47, no. 4, 2010, pp. 181-195. Informa UK Limited, doi:10.3109/10408363.2010.536429.
22. Fletcher, J., Cooper, S., Ghosh, S. and Hewison, M. (2019). The Role of Vitamin D in Inflammatory Bowel Disease: Mechanism to Management. Nutrients, 11(5), p.1019.
23. Flynn, Lisa et al. "Effects of Vitamin D Deficiency in Critically Ill Surgical Patients". *The American Journal of Surgery*, vol 203, no. 3, 2012, pp. 379-382. Elsevier BV, doi: 10.1016/j.amjsurg.2011.09.012.

24. Frigstad, Svein Oskar et al. "Vitamin D Deficiency in Inflammatory Bowel Disease: Prevalence and Predictors in A Norwegian Outpatient Population". *Scandinavian Journal of Gastroenterology*, vol 52, no. 1, 2016, pp. 100-106. Informa UK Limited, doi:10.1080/00365521.2016.1233577.
25. Graedel, Lena et al. "Vitamin D Deficiency Strongly Predicts Adverse Medical Outcome Across Different Medical Inpatient Populations". *Medicine,* vol 95, no. 19, 2016, p. e3533. Ovid Technologies (Wolters Kluwer Health), doi:10.1097/md.0000000000003533.
26. Grenade, Neil et al. "Use of A Loading Dose of Vitamin D for Treatment Of Vitamin D Deficiency In Patients With Intestinal Failure". *Journal of Parenteral and Enteral Nutrition*, vol 41, no. 3, 2016, pp. 512-516. Wiley, doi:10.1177/0148607115625220.
27. Han, Yoo Min et al. "Risk Factors for Vitamin D, Zinc, And Selenium Deficiencies in Korean Patients with Inflammatory Bowel Disease". *Gut and Liver*, vol 11, no. 3, 2017, pp. 363-369. The Editorial Office of Gut and Liver, doi:10.5009/gnl16333.
28. Holick, Michael F. "Vitamin D Deficiency". New England Journal of Medicine, vol 357, no. 3, 2007, pp. 266-281. *New England Journal of Medicine* (NEJM/MMS), doi:10.1056/nejmra070553.
29. Ifigenia, P et al. “Effect of Short-Term Vitamin D Correction on Hepatic Stenosis as Quantified by Controlled Attenuation Parameter” *Journal of Gastrointestinal liver disease*, 2016.
30. Jiang, Xia et al. "The Genetics of Vitamin D". *Bone,* 2018. Elsevier BV, doi: 10.1016/j.bone.2018.10.006.
31. Keane, Jeremy et al. “Vitamin D and the Liver- Correlation or cause?”. *Nutrients*,2018. 10, 496; doi:10.3390/nu10040496.

32. Feldman, David et al. Vitamin D. *Elsevier Academic*, 2008. pp. 117–134. ISBN 978-0122526879.
33. Lund-Nielsen, Josephine et al. "Vitamin D and Inflammatory Bowel Disease: Mendelian Randomization Analyses in The Copenhagen Studies and UK Biobank". *The Journal of Clinical Endocrinology & Metabolism,* vol 103, no. 9, 2018, pp. 3267-3277. The Endocrine Society, doi:10.1210/jc.2018-00250.
34. Margulies, Samantha L et al. "Vitamin D Deficiency in Patients with Intestinal Malabsorption Syndromes - Think in And Outside the Gut". *Journal of Digestive Diseases*, vol 16, no. 11, 2015, pp. 617-633. Wiley, doi:10.1111/1751-2980.12283.
35. McKinney, Jason D. et al. "Relationship Between Vitamin D Status and ICU Outcomes in Veterans". *Journal of The American Medical Directors Association*, vol 12, no. 3, 2011, pp. 208-211. Elsevier BV, doi: 10.1016/j.jamda.2010.04.004.
36. Meehan, Meghan, and Sue Penckofer. "The Role of Vitamin D in The Aging Adult.". Journal of Aging and *Gerontology*, vol 2, no. 2, 2014, pp. 60-71. Savvy Science Publisher, doi:10.12974/2309-6128.2014.02.02.1.
37. Moore, D. D. et al. "International Union of Pharmacology. LXII. The NR1H And NR1I Receptors: Constitutive Androstane Receptor, Pregnene X Receptor, Farnesoid X Receptor, Farnesoid X Receptor Beta, Liver X Receptor, Liver X Receptor Beta, And Vitamin D Receptor". *Pharmacological Reviews*, vol 58, no. 4, 2006, pp. 742-759. American Society for Pharmacology & Experimental Therapeutics (ASPET), doi:10.1124/pr.58.4.6.
38. Mudambi, K. and Bass, D. (2018). Vitamin D: a brief overview of its importance and role in inflammatory bowel disease. Translational Gastroenterology and Hepatology, 3, pp.31-31.

39. Mueller, C. (2012). The A.S.P.E.N. Adult Nutrition Support Core Curriculum. 2nd ed. Silver Spring: American Society for Parenteral and Enteral Nutrition, pp.125-126.
40. Nair, Rathish. "Vitamin D: The "Sunshine" Vitamin". *J Pharmacol Pharmacother*, vol 3, no. 2, 2012, pp. 118-123., doi:10.4103/0976-500X.95506. Accessed 26 Oct 2018.
41. Napartivaumnuay, Navaporn, and Leah Gramlich. "The Prevalence of Vitamin D Insufficiency and Deficiency and Their Relationship with Bone Mineral Density And Fracture Risk In Adults Receiving Long-Term Home Parenteral Nutrition". *Nutrients*, vol 9, no. 5, 2017, p. 481. MDPI AG, doi:10.3390/nu9050481.
42. Nielsen, Ole Haagen et al. "Managing Vitamin D Deficiency in Inflammatory Bowel Disease". *Frontline Gastroenterology*, 2019, pp. flgastro-2018-101055. BMJ, doi:10.1136/flgastro-2018-101055.
43. "Office of Dietary Supplements - Vitamin D". Ods.Od. Nih.Gov, 2019, https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/.
44. Palacios, Cristina, and Lilliana Gonzalez. "Is Vitamin D Deficiency A Major Global Public Health Problem?". *The Journal of Steroid Biochemistry and Molecular Biology*, vol 144, 2014, pp. 138-145. Elsevier BV, doi: 10.1016/j.jsbmb.2013.11.003.
45. Pfotenhauer, Kim M., and Jay H. Shubrook. "Vitamin D Deficiency, Its Role in Health and Disease, And Current Supplementation Recommendations*". The Journal of The American Osteopathic Association*, vol 117, no. 5, 2017, p. 301. American Osteopathic Association, doi:10.7556/jaoa.2017.055.
46. Pittas, Anastassios G. et al. "Role of Vitamin D in Adults Requiring Nutrition Support". *Journal of Parenteral and Enteral Nutrition*, vol 34, no. 1, 2009, pp. 70-78. Wiley, doi:10.1177/0148607109349061.

47. Puccettii, E. et al. "AML-associated translocation products block vitamin D (3)-induced differentiation by sequestering the vitamin D (3) receptor". *Cancer Res*. vol 62, no. 23, 2002, p. 7050.

48. Reboul, Emmanuelle. "Intestinal Absorption of Vitamin D: From the Meal to The Enterocyte*". Food & Function*, vol 6, no. 2, 2015, pp. 356-362. Royal Society of Chemistry (RSC), doi:10.1039/c4fo00579a.

49. Schäffler, Holger et al. "Clinical Factors Are Associated with Vitamin D Levels in IBD Patients: A Retrospective Analysis*". Journal of Digestive Diseases*, vol 19, no. 1, 2018, pp. 24-32. Wiley, doi:10.1111/1751-2980.12565.

50. Sharifi, Amrollah et al. "Vitamin D Status and Its Relation to Inflammatory Markers in Patients with Mild to Moderate Ulcerative Colitis". *Middle East Journal of Digestive Diseases*, vol 10, no. 2, 2018, pp. 84-89. International Society for Phytocosmetic Sciences, doi:10.15171/mejdd.2018.95.

51. Shils, Maurice E. Modern Nutrition in Health and Disease. Lea & Febiger. 2006.

52. Silva, Mariana Costa, and Tania Weber Furlanetto. "Intestinal Absorption of Vitamin D: A Systematic Review*". Nutrition Reviews*, vol 76, no. 1, 2017, pp. 60-76. Oxford University Press (OUP), doi:10.1093/nutrit/nux034.

53. Tan, Bei et al. "Treatment of Vitamin D Deficiency in Chinese Inflammatory Bowel Disease Patients: A Prospective, Randomized, Open-Label, Pilot Study". *Journal of Digestive Diseases*, vol 19, no. 4, 2018, pp. 215-224. Wiley, doi:10.1111/1751-2980.12590.

54. Thomson, Patti, and Donald R. Duerksen. "Vitamin D Deficiency in Patients Receiving Home Parenteral Nutrition". *Journal of Parenteral And Enteral Nutrition*, vol 35, no. 4, 2011, pp. 499-504. Wiley, doi:10.1177/0148607110381269.

55. Ulitsky, Alex et al. "Vitamin D Deficiency in Patients with Inflammatory Bowel Disease". *Journal of Parenteral and Enteral Nutrition*, vol 35, no. 3, 2011, pp. 308-316. Wiley, doi:10.1177/0148607110381267.

56. Vernia, Tripkovic, Laura et al. "Comparison of Vitamin D2 And Vitamin D3 Supplementation in Raising Serum 25-Hydroxyvitamin D Status: A Systematic Review and Meta-Analysis*". The American Journal of Clinical Nutrition*, vol 95, no. 6, 2012, pp. 1357-1364. Oxford University Press (OUP), doi:10.3945/ajcn.111.031070.

57. Venkata, Krishna V R et al. "Impact of Vitamin D on The Hospitalization Rate of Crohn's Disease Patients Seen at A Tertiary Care Center". *World Journal of Gastroenterology*, vol 23, no. 14, 2017, p. 2539. Baishideng Publishing Group Inc., doi:10.3748/wjg. v23.i14.2539.

58. Vernia, Piero et al. "Inadequate Sunlight Exposure in Patients with Inflammatory Bowel Disease". *Journal of Digestive Diseases*, vol 19, no. 1, 2018, pp. 8-14. Wiley, doi:10.1111/1751-2980.12567.

59. Wu, Shaoping et al. "Vitamin D Receptor Pathway Is Required for Probiotic Protection in Colitis". *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol 309, no. 5, 2015, pp. G341-G349. American Physiological Society, doi:10.1152/ajpgi.00105.2015.

60. Yang, Fuwei et al. "The Value of Severe Vitamin D Deficiency in Predicting the Mortality Risk of Patients with Liver Cirrhosis: A Meta-Analysis". *Clinics and Research in Hepatology and Gastroenterology*, 2019. Elsevier BV, doi: 10.1016/j.clinre.2019.03.001.

61. Wang, Ningjian. "Vitamin D and Nonalcoholic Fatty Liver Disease: Bi-Directional Mendelian Randomization Analysis". *Ebio medicine*, vol 28, 2018, pp. 187-193., doi: 10.1016/j.ebiom.2017.12.027. Accessed 18 July 2019.

62. Zaidi, Syed Asher Hussain et al. "Vitamin D Deficiency in Medical Inpatients: A Retrospective Study of Implications of Untreated Versus Treated Deficiency". *Nutrition and Metabolic Insights*, vol 9, 2016, p. NMI.S33747. SAGE Publications, doi:10.4137/nmi.s33747.
63. Zammit, Stefania et al. "Vitamin D Deficiency in A European Inflammatory Bowel Disease Inception Cohort: Am Epo-IBD Study". *European Journal of Gastroenterology & Hepatology*, 2018, Accessed 26 Oct 2018.

Appendix I

Conclusion Grading Table					
Strength of Evidence Elements	**Grades**				
	I **Good**	**II** **Fair**	**III** **Limited**	**IV** **Expert Opinion Only**	**V** **Grade Not Assignable**
Quality Scientific rigor/validity Considers design and execution	Studies of strong design for question Free from design flaws, bias and execution problems	Studies of strong design for question with minor methodological concerns, OR Only studies of weaker study design for question	Studies of weak design for answering the question OR Inconclusive findings due to design flaws, bias or execution problems	No studies available Conclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research	No evidence that pertains to question being addressed
Consistency Of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most	Inconsistency among results of studies with strong design, OR Consistency with minor exceptions across studies of weaker design	Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies	Conclusion supported solely by statements of informed nutrition or medical commentators	NA
Quantity Number of studies Number of subjects in studies	One to several good quality studies Large number of subjects studied Studies with negative results have sufficiently large sample size for adequate statistical power	Several studies by independent investigators Doubts about adequacy of sample size to avoid Type I and Type II error	Limited number of studies Low number of subjects studied and/or inadequate sample size within studies	Unsubstantiated by published research studies	Relevant studies have not been done
Clinical Impact Importance of studied outcomes Magnitude of effect	Studied outcome relates directly to the question Size of effect is clinically meaningful Significant (statistical) difference is large	Some doubt about the statistical or clinical significance of the effect	Studied outcome is an intermediate outcome or surrogate for the true outcome of interest OR Size of effect is small or lacks statistical and/or clinical significance	Objective data unavailable	Indicates area for future research
Generalizability To population of interest	Studied population, intervention and outcomes are free from serious doubts about generalizability	Minor doubts about generalizability	Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied	Generalizability limited to scope of experience	NA