

A Vitamin D Protocol Post Liver Transplantation

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Abstract

Adults with compromised liver function are inherently deficient and especially vulnerable to the consequences of vitamin D deficiency. Consequences of vitamin D deficiency include liver disease progression, infection, and graft failure. A vitamin D supplementation protocol is proposed to systematically optimize serum vitamin D levels in both pre and post liver transplanted patients. This quasi-experimental study used convenience sampling for 45 post liver transplant patients at a large academic facility. The measurable outcome in the three-month study was the serum 25-hydroxy vitamin D levels post supplementation protocol. Seventy-eight percent of patients reached minimum guideline levels using the protocol with an average increase of serum vitamin D of 13.8ng/mL. Long-term outcomes of clinical significance may include decreased incidence of acute cellular graft rejection and infections in the immune-compromised patient. Optimizing vitamin D in vulnerable patient populations such as chronic liver disease and the immune-suppressed post-transplanted patient has the potential to curtail complications of vitamin D deficiency. As a result, employing a vitamin D protocol can have a favorable impact on patient quality of life, safety, and healthcare spending.

Keywords: vitamin D, ergocalciferol, cholecalciferol, liver disease, vitamin D deficiency, clinical guidelines, metabolic syndrome, hepatic osteodystrophy, non-alcoholic fatty liver disease, mortality, and sustained virologic response

A VITAMIN D PROTOCOL POST LIVER TRANSPLANTATION

A Vitamin D Protocol Post Liver Transplantation

Vitamin D deficiency (VDD) is endemic among patients with end-stage liver disease listed for transplantation (Abu-Mouch, Fireman, Jarchovsky, Zeina, & Assy, 2011; Chaney, Heckman, Diehl, Meek, & Keaveny, 2015; Stein & Shane, 2011; Zhang et al., 2016) and in those with liver disease. This deficiency has been reported as high as 91% (Chaney et al., 2015; Choudhary et al., 2011). Vitamin D (VD) has a number of pleiotropic effects including anti-inflammatory properties, anti-apoptosis, anti-fibrosis, regulation of function in the kidney, heart, and immune system, and it maintains homeostasis by regulation of hormone secretion, cell proliferation, and differentiation (Lai & Fang, 2013). Research outlines the merits of vitamin D supplementation (VDS) in patients with chronic liver disease (CLD) of various etiologies (Anty et al., 2014; DiCarlo et al., 2015; Eliades & Spyrou, 2015; Fernandez-Fernandez, Linares-Torres, Matias, Jorquera-Plaza, & Olcoz-Goni, 2015; Stokes, Krawczyk, Reichel, Lammert, & Grunhage, 2014). Cited benefits can be stratified into areas such as the immune system (innate and adaptive), metabolic disorders, bone health, and all-cause mortality (Iruzubieta, Teran, Crespo, & Fabrega, 2014; Stokes, Volmer, Grunhage, & Lammert, 2013; Villar, Del Campo, Ranchal, Lampe, & Romero-Gomez, 2013).

Clinical practice guidelines from three different professional organizations recommend VDS in high-risk populations such as adults with CLD and post liver transplantation, suggesting detailed dosing schedules (Lucey et al., 2013; Holick et al., 2011). Currently, patients are sporadically supplemented with weekly doses of ergocalciferol (vitamin D₂) in the student investigator's (SI) practice. However, cholecalciferol (vitamin D₃) has been shown to have a more effective increase on serum 25(OH)D (Logan, Gray, Peddie, Harper, & Houghton, 2013) Mangoo-Karim et al., 2015; Osborn & Germann, 2011).

Project Background

Significance of the Topic

Vitamin D deficiency (VDD) is prevalent in patients with liver failure, as well as in organ recipients, and can persist long after transplantation (Courbebaisse et al., 2014; Thiem et al., 2013). Immune system compromise, hyperparathyroidism, bone loss, fracture, muscle weakness, falls, insulin resistance, hypertension, and malignancy have all been associated with VDD (Stein et al., 2009). In patients with cirrhosis, the incidence of severe VDD (<25ng/mL) increases with worsening synthetic liver dysfunction (Kitson & Roberts, 2012; Zhang et al., 2016). With respect to patient safety, therapeutic VD levels have been shown to increase strength (Bischoff-Ferrari et al., 2004; Bischoff-Ferrari et al., 2012), and although it has not shown to reduce falls in the vitamin D-optimized population, it is thought to have an effect on muscle strength in those that are severely deficient (Gillespie et al., 2012).

Economic significance. Vitamin D can confer health benefits to the general population as well as reduce the risks that are consequential of vitamin D deficiency (Grant et al., 2009). Diseases such as diabetes mellitus, cardiovascular disease, various cancers, bacterial and viral infections, and immune system dysfunction involve vitamin D deficiency and have a tremendous economic impact on society (Grant et al., 2009). With numerous comorbidities involving vitamin D deficiency, the financial burden of sub-optimal serum levels has a significant economic effect. Economic burden represents direct medical costs such as screening and treatment, as well as indirect costs involving the effects of comorbidities and mortality (Grant et al., 2009). Successful optimization of serum 25(OH)D levels of patients to 40 ng/mL has the potential to reduce the overall direct economic strain of disease by 11.4%, or \$118 million and would decrease the indirect economic obligation of disease by \$93 million (Grant et al., 2009). In turn, this would

result in a comprehensive reduction in economic burden of disease by 17.7%, or \$211 million (Grant et al., 2009).

Policy and health system significance. Vitamin D deficiency is considered endemic, and changes in public policy are in order to help at-risk groups maintain an optimal level through appropriate sunlight exposure, fortified foods, and supplementation (Holick, 2010). Currently, the United States Preventative Services Task Force (USPSTF) lists the evidence for testing vitamin D in asymptomatic adults as “inconclusive” (“USPSTF,” 2014). However, this is not always an accurate indicator of who needs to be tested. In a cohort study of healthy medical residents and students at a Boston hospital, 32% were found to be VD deficient despite daily intake of VD (400IU) and a glass of vitamin D fortified milk (Holick, 2010). Public policies are needed to ensure sufficient intake of vitamin D in all industrialized countries (Holick, 2010).

Local Issue of Vitamin D Deficiency

It is well established that compromised liver function will affect an individual’s ability to synthesize VD (Arteh, Narra, & Nair, 2010; Autier & Gandini, 2007; Krol et al., 2014), thus causing vitamin D deficiency in patients with liver disease. The targeted population in this Doctor of Nursing Practice (DNP) project are transplanted patients with sub-optimal serum 25(OH)D levels. The intention is to supplement these patients who are especially at risk for complications of the VDD. The pre-transplant population has advanced disease, and the post population is vulnerable to infections and graft rejection (Kitson & Roberts, 2012).

Considering Diversity

The city of Los Angeles is home to one of the most diverse populations in the country. The demographics of the liver transplant service at the study site, while not representing all communities, reflects much of the city’s diverse population. The Hispanic population is the

largest minority contingent, and language barriers are prevalent. Therefore, education and social support dynamics must be considered. Additionally, darker skin is more common in this population and interferes with natural vitamin D absorption from the sun (Mangoo-Karim et al., 2015). Despite living in the solar-rich environment of southern California, pre-treatment levels of vitamin D tend to be lower in darker-skinned patients than in Caucasians (Mangoo-Karim et al., 2015). The Asian population born outside of the US brings an otherwise rare etiology for transplantation which is hepatitis B. Patients with an etiology of hepatitis B must take life-long medications that are known to adversely affect bone health and place them at risk for fractures (Holick et al., 2011).

Problem and Purpose

Problem Statement

End-stage liver disease creates a host of comorbidities, one being compromised metabolism of vitamin D leading to severely deficient levels. Although studies have highlighted numerous benefits that supplementation would confer in this population, few venture to recommend standardizing a protocol that would assure therapeutic levels. This project encompassed a vitamin D3 (cholecalciferol) supplementation protocol that was developed and implemented for patients with liver disease prior to transplantation with the intention of continuing surveillance/supplementation post transplantation. Although both pre and post transplanted patients receive supplementation, this study focused only on the post-transplanted patient's response to this dosing schedule. This protocol replaces the previously used vitamin D2 (ergocalciferol) dosing as evidence shows the superiority of cholecalciferol in improving serum 25(OH)D levels (Logan et al., 2013; Osborn & Germann, 2011).

Catalyzing Change

Vitamin D has long been sporadically checked in the SI's patient population. On the inpatient area of the department, the nurse practitioners are the primary providers that initiate and discontinue medications. Awareness of vitamin D deficiency has not been optimal, therefore leading to patients with sub-optimal levels, as they are not always evaluated in their respective clinics. A combination of a persistent and thorough registered dietician along with the SI's goal of translating evidence into practice provided the foundation for the current DNP project.

The primary purpose of this DNP project was to employ a vitamin D3 dosing protocol developed from the input of a multi-disciplinary team and subsequently assess serum levels for the protocol's effectiveness in patients with end-stage liver failure and post liver transplantation in an effort to meet recommended guidelines in these populations.

Facilitators and Barriers

There were more facilitators than barriers in this DNP project. The facilitators included inpatient providers on the liver transplant service, the registered dietician, and liver transplant coordinators. Vitamin D3 is safe and inexpensive, and VD2 is already used in the patient population at the host institution, albeit sporadically. The identified subjects were seen in the outpatient liver clinic and had their 25(OH)D level drawn along with their standard labs. The nutritionist, and liver transplant coordinators in this setting were additional liaisons to the student investigator as well as the main facilitators. Barriers included lack of knowledge about value of project amongst inpatient providers, patient compliance, attitude that it is a low priority intervention in the patient's care, and *buy-in* of providers in outpatient setting. There were no institutional barriers.

Review of the Evidence

PICOTS

In end-stage liver disease patients post transplanted who are deficient in vitamin D, does the implementation of a vitamin D3 protocol improve serum vitamin D level [25(OH)D] to recommended levels during three months on the liver transplant service at a large academic medical center in large metropolitan city?

Search Strategy

The primary databases for the literature search were Medline (PubMed), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane for studies that matched any combination of the following keywords: vitamin D, liver disease, vitamin D deficiency, calcidol, clinical guidelines, metabolic syndrome, hepatic osteodystrophy, non-alcoholic fatty liver disease, mortality, and sustained virologic response. Google Scholar was crosschecked for additional research. Articles published in the last five years were reviewed first, and if highly relevant supporting articles were found to be older, they were also included up to ten years past. Studies were reviewed and those that discussed the relationship between vitamin D deficiency and etiologies of liver disease were included, as well as VDD in the general population. The search was limited to English and Spanish language.

Evidence

VD and the Immune System

Adaptive versus innate immunity. The role of VD in calcium regulation and bone homeostasis is well established (Holick et al., 2011; Lucey et al., 2013); however, recently VD has been recognized as possessing immunomodulatory, anti-inflammatory, and anti-fibrotic properties (Arteh, Narra, & Nair, 2010; Fernandez-Fernandez et al., 2015; Kitson & Roberts, 2012). Additionally, VD has a key function in the management of cell proliferation and differentiation, both extra-skeletal effects that are important in the pathogenesis and treatment of

various etiologies of liver disease (Kitson & Roberts, 2012). With respect to adaptive immunity, VD is an essential regulator of T cell response (up-regulation) to pathogens, and VDS is associated with a lower risk of various autoimmune diseases (Kitson & Roberts, 2012; Putz-Bankuti et al., 2012). In orthotopic liver transplant (OLT) recipients, severe VDD has been associated with moderate to severe acute T-cell mediated rejection (ATCR) with VDS decreasing the incidence of ATCR by as much as 60% (Kitson & Roberts, 2012; Stein & Shane, 2011; Thiem et al., 2013). Reducing graft failure is a highly desirable outcome of VDS as ATCR can predispose a patient to steroid-resistant rejection and graft loss (Cotler, 2016).

VDS has also been shown to increase the effectivity of the innate immune system, thus providing protection against bacterial infections and tuberculosis (Anty et al., 2014; Chowdhury et al., 2014; Putz-Bankuti et al., 2012; Stein & Shane, 2011; Zhang et al., 2016). Notably, cirrhotic patients with severe VDD (<10ng/mL) were independently associated with bacterial infections compared to patients with higher VD levels (Anty et al., 2014; Zhang et al., 2016), and low VD prior to hospitalization was a significant predictor ($p=0.001$) of sepsis in the critically ill (Moromizato et al., 2014).

Sustained virologic response. Chronic hepatitis C infection is one of the main causes of liver disease and increases the risk of developing hepatocellular carcinoma (HCC) by 2-6% per year (Oliviera-Andrade et al., 2009). Recent in vitro studies have shown that VD acts as an antiviral agent that inhibits hepatitis C virus (HCV) production in a human hepatoma cell line (DiCarlo et al., 2015). In patients with HCV that underwent OLT with subsequent recurrent HCV, high rates of sustained virologic response (SVR) were noted in patients receiving VDS (Abu-Mouch, Fireman, Jarchovsky, Zeina, & Assy, 2011; Bitetto et al., 2011; Iruzubieta et al., 2014).

Cancer. Another common theme found in the literature is the association of VDD and cancer development, namely colon, prostate, and breast cancer (Iruzubieta et al., 2014; Stein et al., 2009; Stokes et al., 2014; Villar et al., 2013). VDD is prevalent among cancer patients with one study showing 74% of breast cancer patients to be low in VD and VDS conferring a 15% decrease in mortality among lung cancer patients (Aguirre et al., 2016). Relevant to liver disease is that hepatocellular and intrahepatic cholangiocarcinoma often develop in patients with cirrhosis and is inversely related to levels of VD (Stokes et al., 2013). VD has strong evidence that it promotes anti-apoptotic activity, as well as anti-inflammatory and anti-angiogenic properties that promote cell differentiation and inhibit cancer cell proliferation (Courbebaisse et al., 2014; Stokes et al., 2013).

VD and Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is one result of metabolic syndrome (Kitson & Roberts, 2012). It is a relatively benign condition, and one result of the obesity epidemic that involves some fat infiltration into the liver without inflammation (Chopra, 2016). With a prevalence of up to 30%, NAFLD is rapidly becoming the most common etiology of chronic liver disease in developed western countries (Eliades & Spyrou, 2015; Iruzubieta et al., 2014; Kitson & Roberts, 2012; Lim & Chalasani, 2012). Of the patients with NAFLD, 30% have histological evidence of non-alcoholic steatohepatitis (NASH), the complicated form of NAFLD, risking a high rate of disease progression to cirrhosis (Kitson & Roberts, 2012). Unfortunately, incidence of NAFLD is expected to rise along with the obesity epidemic (Eliades & Spyrou, 2015). NAFLD is generally known to be associated with at least one metabolic syndrome characteristic, and insulin resistance (IR) has been discussed as a key factor in the development of NAFLD (Del Ben et al., 2014; Iruzubieta et al., 2014).

VD and Hepatic Osteodystrophy

Bone loss associated with liver disease and related treatment is a major issue that is the subject of studies, reviews, and clinical practice guidelines. Also known as hepatic osteodystrophy (HO), this general term defines a group of derangements of bone mineral metabolism found in patients with CLD (Lopez-Larramona, Lucendo, Gonzalez-Castillo, & Tenias, 2011). Bone loss in this population can be severe enough to cause atraumatic fractures, leading to compromised mobility and subsequent decrease in quality of life (Nakchbandi, 2014). However, HO is multifactorial in origin and appears to be the consequence of metabolic bone disease making it impossible to process VD due to the interruption in liver function from disease (Choudhary et al., 2011; Nakchbandi, 2014; Lopez-Larramona, Lucendo, Gonzalez-Castillo, & Tenias, 2011).

VD and Mortality in Liver Disease

In 2013, CLD was ranked twelfth on the leading causes of death in the US and fifth in Europe (Xu, Murphy, Kochanek, & Bastian, 2016). VDD has been associated with higher mortality risk in the general population, and given the prevalence and degree of VDD, patients with CLD are extremely vulnerable to the consequences of VDD as well (Stokes et al., 2014). Furthermore, a large observational study conducted by the US National Health and Nutrition Examination Survey (NHANES) concluded that serum VD levels are inversely related to all-cause mortality (Zhao, Ford, Li, & Croft, 2012). In a meta-analysis of 18 randomized controlled trials, Autier and Gandini (2007) concluded that VDS correlated with a reduction in overall mortality in the general population.

Clinical Practice Guidelines on VDS

The American Association for the Study of Liver Diseases (AASLD) is the main expert body in the US for opinion in the field of liver disease, and providers in hepatology and related practice areas refer to AASLD for guidance on treatment for various liver-related issues. The AASLD, together with the American Society of Transplantation (AST), publishes clinical practice guidelines (CPG) for successful long-term management of the adult liver transplant recipient. In the guidelines, the benefit from VDS in the post transplanted patient are addressed and include improved sustained virologic response for patients with HCV, immune system fortification against both infection and graft rejection, and a decreased incidence of malignancies (Lucey et al., 2013). Moreover, guidelines from the AASLD, the AST, and the Endocrine Society recommended maintaining a minimum of 30ng/mL serum VD (Holick et al., 2011). Additionally, patients on steroids, anti-fungals, and certain antiviral medications used for prevention of hepatitis B recurrence are also at a higher risk for VDD and should be supplemented two to three times more than their age-group requires (Holick et al., 2011).

The Case for VD Supplementation

A recent resurgence of the benefits of VD on overall health of the general population contributed to a meta-analysis of 25 randomized, placebo-controlled trials evaluating the dose response relationship of oral vitamin D3 (Jarrett, Ducasa, Buller, & Berwick, 2014). A regression analysis of all reviewed studies showed a correlation of 61% which supported a consistent dose-response relationship independent of various confounders (Jarrett et al., 2014). Additionally, the researchers found that healthy and ill individuals did not vary on response to dose, supporting a generalizable dosing schedule (Jarrett et al., 2014). In a meta-analysis of randomized controlled trials of oral vitamin D supplementation, it was found that high-dose VDS ($\geq 800\text{IU/day}$) was

more beneficial in the prevention of hip fracture and any nonvertebral fracture in people 65 years and older (Bischoff-Ferrari et al., 2012).

Theory, Change Process

The Diffusion of Innovations (DOI) theory is the most prominent example of classical change theory that describes the natural process of innovation adoption (Macdonald, Graham, & Grimshaw 2014). The DOI theory examines the application of proven interventions into daily practice and contends that the rate of innovation is attributed to characteristics of both the product and the people meant to adopt the product (Nilsen, 2015). The DOI theory has been used to introduce new information in a variety of areas such as nursing, medicine, marketing, and technology. In nursing, it has been used to examine the nurses' role in vaccine uptake (Rosen & Goodman, 2014), implementing a pain medication protocol for nurses in the ED (Hadorn, Comte, Foucault, Marin, & Hugli, 2015), and AIDS/HIV prevention (Melkote, Moore, & Velu, 2014).

Theory Concepts

The first concept, adoption, is the act of employing an innovation systematically and is a salient concept in the DOI process (Nilson, 2015). This DNP project is prescriptive in nature; therefore, success is contingent on evidence adoption by other providers in the liver transplant department, as well as patient compliance. Without adoption, evidence based practice (EBP) would remain an elusive concept confined to the dusty annals of nursing and medical journals. Communication is a fundamental concept facilitating leadership and teamwork which are the most important constructs for planned change (Mitchell, 2013). The DNP project must communicate the discrepancy in care that exists in addition to the negative impact that such a discrepancy has on the patient population.

Methods

Institutional Review Board

An IRB (Institutional Review Board) application was first filed at the University of California, Los Angeles. As a result of this process, UCLA did not feel review was required due to the nature of the study. An IRB was then filed with the University of Missouri, Kansas City who categorized the project as not human subjects research (see appendix I).

Ethical Issues

Informed consent was provided in English or Spanish, and subjects were given the opportunity to participate without coercion or decline. Patients that didn't speak English as a primary language understood that they would receive the same treatment regardless of participation in the DNP project. Standard HIPAA regulations were observed. Potential conflicts of interest included SI bias when recruiting patients to participate.

Funding

Funding was projected to be minimal for this DNP project, as the intervention was a component of the existing plan of care. The 25-hydroxy vitamin D serum check was part of the standard lab draw and was expected to be covered by the patient's insurance. The cost of the vitamin D3 pills was minimal for a 12-week supply, approximately \$10, and covered the duration of the protocol. Vitamin D3 was also covered by some of the patients' insurance, and others were able to pay out of pocket. The patients followed up at regularly scheduled appointments with their hepatologist or primary care provider, avoiding additional costs of a clinic or lab visit. For the project, the cost of the advance practice registered nurse (APRN) was \$631.00.

Setting and Subjects

The setting was a large academic tertiary facility located in a large metropolitan city on the west coast. This facility has one of the country's largest liver transplant programs with 163 patients receiving livers in 2014 ("US Liver Transplant Centers," 2016). Inclusion criteria were post-transplanted less than six months with a serum 25(OH)D of less than 30ng/mL and the ability to understand and speak English or Spanish. Exclusion criteria were 25(OH)D greater than 30ng/mL, post-transplantation greater than three years, need of translator services in languages other than English or Spanish, and patients that are currently on Vitamin D supplements. Patients with a documented history of poor medication compliance were excluded. Convenience sampling was used and a total of 48 patients were included in the project.

Evidence Based Practice Intervention

Patients with liver disease are inherently at risk for severe VDD and the various comorbidities include compromised immune system function, metabolic disorders, and hepatic osteodystrophy (Courbebaisse et al., 2014; Thiem et al., 2013). Clinical practice guidelines endorse a minimal level of 30ng/mL for serum 25-hydroxy vitamin D for patients prior to and after liver transplantation (Holick et al., 2011; Kitson & Roberts, 2012). This DNP project proposed a VDS protocol with the intention of fulfilling clinical practice guideline recommendations. Clinical providers on the in-patient liver transplantation service were educated on the protocol by the SI; however, the SI identified all eligible subjects through a chart review. A newly admitted patient with pre or post-transplanted status had 25-hydroxy vitamin D drawn along with standard labs. If the patient was found to be lower than 30ng/mL, the protocol was initiated. Once the protocol was an established part of care, any provider who was caring for the patient could order it. Long-term effects such as incidence of acute cellular graft rejection or fractures can be tracked and reviewed in future cohort studies.

Intervention steps. The DNP project started in June 2016 with the IRB application to UCLA Medical Center and UMKC. July 2016 was slated for candidate identification of post liver transplant; however, this was delayed due to availability of the renal service. Patient identification started in September 2016 and was accomplished via chart review of patients admitted at the time to the liver transplant service at UCLA Medical Center. The director of post transplant coordinators facilitated a weekly clinic schedule which allowed the SI to review which transplanted patients needed VDS. As eligible patients were identified weekly, informed consent occurred on a rolling basis and was acquired in person by the SI at the clinic or occasionally by telephone. The initiation of the protocol started September 2016; and all identified patients after that time started the new VD supplementation intervention ordered by SI. Recruitment continued until January 2017 at which point 47 patients were included. The SI tracked the 12-week time frame for each individual. The patients returned to clinic at their regularly scheduled appointment which was usually within 1-2 weeks of the 12 week treatment course.

EBP Model, The Clinical Scholar Model

The Clinical Scholar Model (CSM) was developed to promote thoughtful inquiry, educate direct care providers such as nurses and advance practice nurses (APRN), promote EBP mentorship, and conduct research in a clinical setting (Melnyk & Fineout-Overholt, 2015). The model can help identify problems in a setting, key stakeholders, and areas in need of improvement (Honess, Gallant, & Keane, 2009). It also provides a framework to examine both internal and external evidence (Honess et al., 2009). One of the goals of the CSM is to review current practices in direct care in favor of an intervention that has evidence to be beneficial (Melnyk & Fineout-Overholt, 2015; Honess et al., 2009).

With respect to the project, the CSM aligns well with the inquiry in this project which questions the current sporadic supplementation of vitamin D and seeks out guidelines that recommend a minimum serum level. Both internal evidence, which is the vitamin D levels prior to supplementation as well as serum levels after supplementation, and external evidence examined within the project. The DNP project was presented to the liver transplant APRN colleagues as well as the staff nurses who care for these patients. The hope was that the example of challenging an existing practice with an evidence based intervention would encourage nurses on the unit to develop this same clinical inquiry for their own nursing practice.

Study Design

The non-randomized nature of this DNP project inherently makes this a quasi-experimental study. Serum vitamin D levels were analyzed in the post-transplanted population. The patients started the vitamin D supplementation protocol during hospitalization, and VD levels were assessed at 12 weeks.

Validity

Internal validity. Internal validity for the DNP project was assessed by the laboratory's approach to measuring serum 25-hydroxy vitamin D. Subjects for the study were selected through the convenience method and were assumed to be a representative sample of vitamin D deficient patients that are newly or recently transplanted within the last three years. The main threat to internal validity in this quasi-experimental study was the inability to determine a cause and effect relationship of the intervention (Kleinpell, 2013). However, inclusion criteria for this project were that the subject was vitamin D deficient (<30ng/mL). The patients were not on any other vitamin D supplementation, and as a result, the expected increases in post intervention lab values were attributed to the VDS intervention.

External validity. Despite the application of a vitamin D protocol to a specific population, the generalizability of implementing an intervention aimed at improving sub-optimal levels of VD is applicable to the general population. In a meta-analysis of randomized controlled studies, a strong dose-response was found between the amount of supplement and change in serum VD (Jarrett, Ducasa, Buller, & Berwick, 2014). Most important, these results did not change when the review limited the results to studies using healthy individuals (Jarrett et al., 2014). Vitamin D insufficiency and deficiency are widespread in close to half the population of healthy individuals in industrialized countries (Iruzubieta, et al., 2014). In patients with chronic liver disease, this statistic increases up to 93% (Iruzubieta et al., 2014). The DNP project targeted liver disease; however, the dose response and benefits of optimized vitamin D is universal.

Outcomes to be Measured

The primary outcome was to assess the effectiveness of a vitamin D protocol on serum levels in newly transplanted patients. The baseline VD level was compared to the 12-week VD level. Secondary outcomes included evaluating the dose in the patients that were not successfully optimized to 30ng/mL. Patients with lower vitamin D levels may need a more aggressive supplementation protocol, rather than the homogeneous dosing schedule used in this project.

Measurement Instrument

At the SI's facility, the *chemiluminescent immunoassay* (CLIA) is the method of measurement. The CLIA method detects the concentration of vitamin D in a specimen through the quantification of luminescence resulting from chemical reactions (Wang, Wu, Zong, Xu, & Ju, 2012). Validation is performed only by CLIA-licensed facilities ("AACC," 2016). The advantage of the CLIA measurement is that it is highly sensitive with a good level of specificity (Wang et al., 2012).

Quality of Data

Power analysis was calculated given the amount of subjects included. Pre data was the patient's 25-hydroxy vitamin D level. Post data was the repeat lab value of serum 25-hydroxy vitamin D after the 12-week supplementation protocol. The recent meta-analysis by Jarett et al. (2014) lists 25 studies in which subjects were supplemented with VD over various periods of time, and this review was used as a primary source for comparison with the current project results. A more recent randomized controlled trial by Pilz et al. (2016) also provides a reference for expected increase specifically in patients with cirrhosis.

Analysis Plan

Demographics included age, race, and gender. For outcome data, there was an expectation that an increase in serum 25(OH)D would occur. Therefore, a one-tailed t-test was the statistical approach in analyzing the post lab and difference from the VD level prior to the VD supplementation protocol. A p-value of 0.05 was considered statistically significant (Gravetter & Wallnau, 2011) and was the minimal value to determine if the protocol was sufficient in optimizing vitamin D levels in post-transplanted patients.

Results

Setting and subjects

The setting was a large academic tertiary hospital and the corresponding outpatient hepatology clinics in a large metropolitan city on the west coast. Subjects were post liver transplantation of three years or less with normal renal function (GFR >30) found to be VDD as defined by a serum 25-OH D level of less than 30ng/dL. Participant (n=45) ages ranged from 48-70 years old and were Hispanic (50%), Caucasian (28%), African-American (11%), and Asian

(11%). The project racial breakdown mirrored the city's racial demographic as reported in the 2010 US census ("US Census," 2016). The gender distribution was 51% male and 49% female.

Intervention Course

Eligible patients were identified using the inpatient census at the beginning of the project period in September 2016. These patients were approached and educated on the importance of vitamin D supplementation by the SI. If the patient was not currently taking vitamin D, cholecalciferol (vitamin D3) 2500IU/day was added to the medication list for a duration of 12 weeks and the start date was noted in the SI's database. To capture additional subjects, the SI approached the post transplant director who then facilitated a weekly outpatient hepatology clinic list with patient names and transplant dates. Approximately 60 patient charts were reviewed every week over the course of four months which resulted in over 900 charts reviewed for the time period. Additional patients were identified on a weekly basis until January 2017 and the SI attended clinic to verbally discuss the new supplement. After the 12-week course of cholecalciferol, patients returned to clinic for their regularly scheduled hepatology appointment and a vitamin D level was obtained. This result was compared to the pre-treatment vitamin D level.

Outcome Data

The primary outcome measure was the difference between the pre and post treatment serum levels of 25(OH)D. The project sample size was to represent at least a power of .8, medium effect, alpha .05 which was 30 patients. Recruitment continued until the 12-week treatment duration would place the patients re-draw date beyond March 2017. The first patients were captured in September 2016 with the last added in January 2017. With these criteria, a total of 48 was added. However, one patient's Endocrinologist changed him to ergocalciferol (D2),

and two patients refused to pay the supplemental cost for the cholecalciferol (D3). Therefore, total subjects were 45.

Statistical analysis. Before patient recruitment began, the SI met with statisticians and discussed an appropriate sample size. It was assumed that approximately 70% of the patients would respond to the dose indicated by Endocrinology as the expectation was that most patients would reach the minimum target level of 30 ng/mL as found in the meta-analysis by Jarrett, Ducasa, Buller & Berwick, 2014 and Pilz et al., 2016. Based on this expectation a power analysis was calculated to determine appropriate sample size that would give a confidence interval (CI) of >90%. Final data indicated that 35 of the 45 patients reached the minimum vitamin D serum level of 30 after VDS, or 78% of the subjects. This was a greater than expected response. Additionally, there was a mean change in serum VD level of 14 ng/mL, however, not all of the patients in the study reached the minimum level of 30 ng/mL.

Additional analysis was performed on the following sub-categories of the study subjects: etiology of liver failure, race, and gender (appendix J). There were some significant differences in how these subcategories responded, namely, Asians had an average increase of over 80% post intervention. Females also appreciably improved post intervention at 81% while males had a 62% change post intervention. There were no significant differences in improvement among the varying etiologies of liver failure.

An estimate of the proportion of responders to the vitamin D intervention, along with a 95% confidence interval, was reported. A one-sided one-proportion z-test was used to evaluate the null hypothesis that 50% or fewer will respond after the vitamin D intervention. A p-value less than 0.05 was considered statistically significant. The sample size of n=45 provides 94% power to detect a true proportion responding after the vitamin D intervention of 78% ($p < 0.001$).

Missing data included the three patients that did not start the cholecalciferol supplementation either due to cost/access or prescription of ergocalciferol by another Endocrine physician.

Discussion

This DNP project raised awareness of the importance of vitamin D in this vulnerable population. Accordingly, co-workers and transplant coordinators were more vigilant with this lab value and benefits to VDS than prior to the project. The vitamin D supplementation protocol was shown to be an effective approach to optimizing serum levels and a large portion of the patients that were started on cholecalciferol reached the minimum dose as recommended by the guidelines.

Study Strengths

The project's success relied heavily on the team approach to facilitating the protocol implementation. Although the SI was the sole person following the patients and their re-draw dates, at many points of time, the post transplant coordinators were contacted regarding details about the patients' access to VD as well as their expected return to clinic. Additionally, the transplant pharmacist was exceedingly helpful and cooperative in sending the supplementation to patients' homes in the event that were not expected back in clinic within 1-2 weeks. The organizational culture at the project site is supportive of quality improvement projects that can improve patient outcomes such as this DNP project.

Because this facility was a large academic hospital, significant resources are available to facilitate this project. This is especially true for the post-transplanted population. These patients are each assigned a post-transplant coordinator that arranges all appointments as well as the contact person for any potential complications. Coworkers on the liver transplant service were

also communicative when questions arose regarding the study subjects' VDS. This allowed for seamless continuance on patient supplementation without compromising the results.

Comparing Results

Comparing dose-response results with published literature was a challenge because there are limited studies dedicated to VDS in liver disease and post transplant. However, as Jarret et al., 2014 observed in their meta-analysis of 36 studies, the dose response of VDS did not vary in the absence of chronic disease. Both healthy and chronically ill populations that were analyzed responded well to VDS. The results from this DNP project were compared to the meta-analysis by Jarrett et al. (2014) as well as a randomized controlled trial by Pilz et al (2016) examining vitamin D supplementation, specifically in cirrhotic patients.

In their meta-analysis, Jarrett et al. (2014) plotted the data from 20 of the most reliable and homogeneous studies on a scatter plot which showed a positive correlation between the quantity of oral VD and the change in serum levels. Based on this information, a daily dose of D3 at 2500 units would produce a change in serum level of 16ng/mL. In the RCT of cirrhotic patients, Pilz et al. (2016) employed a daily dose of 2800 units/day and found a mean change from baseline post VDS of 18 ng/mL. The mean change among the DNP project's subjects was 14ng/mL with the 2500 unit daily dose which resembles the meta-analysis' and the RCT findings. Although both studies discussed a minimum normal range of 30 ng/mL, the number of patients that reached that goal post VDS was only reported in ranges rather than in individual cases.

Study Limitations

There are several limitations that should be mentioned with respect to the results. This was a single-center observational study with a small sample size. There are no previous studies,

to the SI's knowledge, that examine post transplant VDS supplementation and dose response. In newly transplanted patients, the exact effect of the functioning liver on the improvement of serum vitamin D is unclear. However, liver disease does not always impair vitamin D receptor function and hypovitaminosis D is thought to be a consequence of poor nutritional intake and sedentary lifestyle (Elangovan, Chahal, & Gunton, 2017).

Serum vitamin D results take over 24 hours to process, therefore when a patient was identified as being deficient, oftentimes they were no longer on site to prescribe VDS. This occasionally caused a problem with respect to access to the vitamin because patients did not want to pay additional money out of pocket to buy VD and returning to clinic was not convenient until the next scheduled appointment. In some cases, the pharmacist was able to mail the vitamin to patient's homes. Post intervention data collection at the indicated time became a major challenge in some cases also due to the patients' return-to-clinic schedule not corresponding with the end of the 12-week period. This could potentially affect the post lab draw result if too much time elapses between last dose and next lab draw.

Despite meticulous communication with Endocrine, at least 2 patients were started on the wrong form of vitamin D (ergocalciferol). Therefore, those patients were taken out of the study. Generalizability factors relevant to broader application of this study include the acuity of the transplanted population in the region of Southern California and the dose of VD recommended. Liver disease and post-transplanted patients may not need the same amount of VDS to achieve the minimum guidelines.

Potential for the vitamin D protocol to become another casualty in the efforts to improve patient outcomes is significant. The liver transplant service is volume heavy with critically ill, complex patients and vitamin supplementation is not high on the list of priorities for care. This

project has raised awareness, and it became clear that despite being a benign intervention, the department stake holders were very cooperative and willing to work on incorporating this protocol into the workflow of both pre and post-transplanted patient care plans. Meetings with the post transplant coordinators were productive, and it was discussed that the outpatient hepatology clinic could be the responsible party for monitoring vitamin D and adjusting doses as needed with surveillance eventually transferring back to the patients' primary care provider.

Efforts to minimize limitations included constant communication with post transplant coordinators, coworkers involved in both inpatient and outpatient settings, and patients themselves. It was sometimes noted that when subjects were readmitted that their vitamin D was not started with the other home medications. This required re-education of the admitting provider. Patients were also reminded of the importance of compliance via telephone or in person. Coordinators were updated on re-draw plans and assisted with ordering labs for those patients that lived outside of the city where the study was carried out.

The limitations affected the results: inability to get the medication to the patient in a timely manner, return to clinic did not always correspond with designated re-draw dates, and awareness, although much improved, was not 100%. Regardless, the quantifiable nature of this project supports VDS and the benefits the review of literature is said to provide.

Interpretation

For the majority of the study subjects, the serum VD level increased to the minimum recommended level as expected. Patients were also very open to prioritizing vitamin D during educational discussions on the benefits to taking this vitamin. Given the pill burden for a post transplant patient, asking the patient to take, yet another, daily supplement was significant. However, patients were generally very supportive and open to doing so if they felt it would

improve their outcomes. With respect to the intervention, there were no unexpected results, and those patients that did not take VD as discussed did not increase their serum VD level. However, one unexpected and notable finding was how closely the convenience sampling of the subjects reflected the racial demographics of the city in which the study was carried out.

Unexpected problems included the challenge of getting the appropriate dose recommended from the pharmacy. Vitamin D typically comes in 1000, 2000, or 5000 IU size pills. Our Endocrine recommendation was 2500IU which was a barrier to getting the dose in the beginning of the project. However, due to the assistance and cooperation of the transplant pharmacist, special orders of the 5000IU pills were placed, and patient used their pill splitter for their daily dose. Additionally, not all local pharmacies carried the 5000IU pill. This limited distribution to when the patients were able to come back to UCLA. At this point, the SI met with the pharmacist to inquire about sending the VD to the patients houses to facilitate initiation. This worked well and facilitated the progression of the DNP project.

Intervention Effectiveness

This DNP project showed the effectiveness of increasing patients' vitamin D serum level to recommended guidelines using a protocol of a daily dose of 2500IU/day for 12 weeks. If patients were compliant and took their VD, it was expected that they would reach the 30 ng/mL level regardless of their baseline prior to supplementation. It was noted that patients who were severely deficient (less than 20 ng/mL) had a greater increase in serum than those that were above 20 but less than 30 ng/mL. This is consistent with the literature that contends that patients who receive the greatest benefit from VDS are those that are severely deficient (Bischoff-Ferrari et al., 2012; Gillespie et al., 2012; Martineau et al., 2017). A VD protocol such as the one

employed in this DNP project (see appendix L) is simple and easy to use in any setting whether it be an outpatient clinic or an inpatient facility.

Intervention Revision

Salient needs on this DNP project included additional assistance with managing the different areas of the implementation and follow-up process. Additional phone calls to patients to follow-up on compliance would have been very helpful, as well as the manpower to review all patients coming to clinic in the weeks to come and their baseline VD level. Raising awareness as to the importance of a requesting behavior is key, and the more people are involved in this, the more effective the message becomes. Occasional emails with current articles extolling the benefits of VD were sent to the post transplant coordinators in an effort to support the continued vigilance on vitamin D in our patients. Additionally, inpatient providers were also updated. Based on the results of this study, an increase of the daily dose of vitamin D would be increased to 3000units/day. This would assure greater increase in serum levels and would also make access easier, as 1000 unit pills are prevalent in most pharmacies.

Health system costs and impacts. The expected impact on this health system was that this protocol would be an easy and effective intervention to address a basic need that fulfilled relevant guidelines to the affected population. Vitamin D supplementation is integrated into public policy through fortified products such as milk and other dairy products (Holick, 2010). For liver disease and post transplanted patients a high pill burden and limited dietary choices can make appropriate vitamin D intake challenging and a protocol that is incorporated into the workflow of patient care was shown to be highly effective in achieving guideline recommended levels of VD.

Estimated costs (appendix A) were edited when the amount of patients involved in the project increased from 30 to 45. Additionally, the initial estimated hours of the SI was lower at 10 than the end result of 20 hours. This impacted the final cost. All but three patients were able to access the vitamin D either through insurance coverage or their willingness to pay out of pocket. Despite solicitation from multiple sources, no funding was granted.

Conclusion

This simple, inexpensive intervention has the potential for a high yield on investment based on the evidence of the protective benefits of vitamin D supplementation in the liver failure and transplanted population. Some of the major effects of optimized VD levels post transplantation include the decreased incidence of acute cellular rejection, decreased rate of infection, and reduced incidence of fracture (Kitson & Roberts, 2012; Moromizato et al., 2014; Nakchbandi, 2014). Vitamin D supplementation using ergocalciferol was the current approach at project site among liver transplant providers. The move towards cholecalciferol was appropriate given the evidence that it has shown to improve serum levels more effectively than ergocalciferol (Logan et al., 2013; Mangoo-Karim et al., 2015; Osborn & Germann, 2011).

Further Studies

Given the limited time frame for which to evaluate the effects of long-term optimized VD, further studies will be needed to determine if the VDS and subsequent optimization of serum 25(OH)D can curtail the incidence of graft rejection, infection, fractures, and other consequences of VDD. Tracking fresh liver transplanted patients that are maintained with VDS and their incidence of graft failure in comparison, retrospectively, with patients who were noted to be consistently VDD is one example of how VDS can be confirmed as an essential component of treatment in this population.

The accumulated findings of this DNP project will be shared with the providers at the inpatient practice at the project site, as well as the patient's hepatologist, liver transplant coordinators, registered dietitians, and healthcare providers. Additionally, the project was presented at the annual California Association of Nurse Practitioner's educational conference in San Francisco and the UMKC Health Sciences Student Research Summit in Kansas City, Missouri. Project dissemination will be essential in raising awareness and subsequently addressing vitamin D deficiency. It will also serve to provide education on the ease of incorporating a protocol for supplementation, hence, improving patient outcomes in the future.

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Appendix A

Project Cost-Analysis

Cost Analysis

Direct costs	Unit cost	Quantity	Total
Serum 25-hydroxy vitamin D post supplementation lab draw	\$30	45 patients	\$1350
Vitamin D3 supplement for 12 weeks	\$10	45 patients	\$450
Student investigator	\$63.21/hr	20hrs	\$1264.20
Total Program Cost			\$3064.20

A VITAMIN D PROTOCOL POST LIVER TRANSPLANTATION

Appendix B

Definition of Terms

Cholecalciferol: also known as vitamin D3, this is an animal based compound (Mangoo-Karim et al., 2015).

Clinical practice guidelines from the American Association for the Study of Liver Diseases, The American Transplant Society, and the Endocrine Society recommend levels of vitamin D are 30ng/mL and above (Holick et al., 2011; Lucey et al., 2013)

Ergocalciferol: also known as vitamin D2, this is a plant-based sterol (Mangoo-Karim et al., 2015).

Large academic hospital in this study: University of California, Los Angeles

Vitamin D deficiency: serum 25(OH)D level of less than 20ng/mL (Drezner, 2016).

Vitamin D insufficiency: serum 25(OH)D level of less than 30ng/mL (Drezner, 2016).

Appendix C: Review of Evidence Table

First author, Year, Title, Journal	Purpose	Research Design ¹ , Evidence Level ² & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
VDS & THE IMMUNE SYSTEM						
Zhang, C., 2016 <i>Enhanced LL-37 expression following vitamin D supplementation in patients with cirrhosis and spontaneous bacterial peritonitis</i> Liver International	Further investigate hypothesis that innate immunodeficiency in peritoneal cavity caused by low VD leads to vulnerability to bacterial infections with unfavorable outcomes	Quantitative, observational, cohort, Level IV Variables: LL-37 expression, VD levels, presence of spontaneous bacterial peritonitis (SBP)	N=119 patients with chronic liver disease (CLD) in a single center academic facility in China	Lab values of serum vitamin d (25-OH-VD), vitamin D receptor (VDL) and LL-37 in peritoneal leucocytes were detected and compared to those without SBP	VDD was found in all cirrhotic patients. Low VD levels inhibit the LL-37 response of peritoneal macrophages, thus making the patient more vulnerable to SBP. This can be remedied with vitamin D supplementation (VDS). Univariate analysis was used.	Clinical significance: Supports VD supplementation Limitations: Authors did not highlight any, however single center studies are always considered a limitation, as it is not necessarily reflective of worldwide population. Geographic location in northern region has less sunlight, affects VD levels to higher degree
DiCarlo, P. 2015, <i>Vitamin D and osteoporosis in HIV/HCV coinfectd patients: A literature review</i> International Journal of Endocrinology	Summarizes prevalence of VDD in HIV/HCV coinfectd, association between VD and liver disease and discusses impact of inexpensive therapy on reducing liver fibrosis and improving sustained virologic response	IRR level VII Variables: VD levels, severity of liver disease, virologic response to HCV treatment, bone mineral density,	12 articles were included: 10 original studies, 1 meta-analysis/SR, 1 review manuscript. Of these: 5 were cross-sectional, 2 prospective cohort, 3 retrospective	Serum VD levels	VD supplementation can be considered an inexpensive therapeutic option to lower HCV-related fracture risk	Clinical significance: Supports VD supplementation Limitations: no RCT to examine those with VD supplementation and those without

	rate					
Fernández-Fernández, N. 2015, <i>Vitamin D deficiency in chronic liver disease, clinical epidemiological analysis and report after vitamin d supplementation</i> Gastroenterología y Hepatología	Discover the frequency of vitamin d deficiency in patients with chronic liver disease (CLD) and whether VD supplementation influences plasma levels and is associated with improved liver function	Quantitative, observational, cohort, Level IV Variables: vitamin d supplementation and liver function (Child-Pugh, MELD)	N=94 patients with CLD (45 of which had cirrhosis) in an academic facility in Leon, Spain	Lab values of serum vitamin d (25-OH-VD), platelet counts, and albumin levels	94% of patients with significant improvement were seen in platelet and albumin levels (p <0.5) and functional status assessed by Child-Pugh scale (p <0.5)	Clinical significance: Supports VD supplementation Limitations: Time of year: winter and less hours of sunlight may have affected results, long term follow-up on VD levels: how long can supplementation sustain therapeutic levels? Lacked resources to determine if level of fibrosis was associated with VD levels
Anty, R., 2014, <i>Low levels of 25-hydroxy vitamin D are independently associated with the risk of bacterial infection in cirrhotic patients</i> Clinical and Translational Gastroenterology	Compare hospitalized cirrhotic patients' serum levels of VD with infection to those without infection	Quantitative, observational, prospective cohort study, level IV Variables: serum VD, presence of infection (UA, bacteremia, PNA, SBP, bone infection)	N=88 patients with cirrhosis admitted in a single-center academic facility in Nice, France	Serum VD, Child-Pugh score, C-reactive protein, ALT level	More patients with severe VDD were infected (54 vs. 29%, P=0.02) More infected patients had severe VDD compared to those not infected (71 vs. 46%, P=0.019)	Clinical significance: severe deficiency in 25-OH VD was a notable independent factor correlating with infection. Supports VDS. Limitations: Single-center study, small patient pop'n
Courbebaisse, M., 2014 <i>VITamin D supplementation in renal transplant recipients (VITALE): a prospective, multicentre,</i>	Assess benefit and safety of high-dose VD in post renal transplant patients	Quantitative, double-blind, placebo controlled, RCT level I (ongoing study) Variables: VD doses, serum VD. Evaluate the risks	N=640 renal transplant recipients in a multi-center, carried out in 30 different transplant centers in Paris, France. Recruitment is to end in 2016.	Serum VD, lipid profile, LFT, PTH, bone mineral density (BMD), fasting blood sugar	Previous study by same group showed that intensive VD is well tolerated in renal transplant recipients, using this information, a dose specific result from	Clinical significance: Potential to be a hallmark study given the duration (over 2 years) and quality of study. It is understood that

<p><i>double-blind, randomized trial of vitamin D estimating the benefit and safety of vitamin D3 treatment at a dose of 100,000 UI compared with a dose of 12,000 UI in renal transplant recipients: study protocol for a double-blind, randomized, controlled trial.</i> Trials</p>		<p>and benefits of high dose versus low dose VD, with endpoints of de novo DM, CV, bone fracture, or death</p>			<p>the VITALE study is expected, with additional information on development of de novo DM, CV, bone fracture, or death</p>	<p>VDS is beneficial, however, more specifics on dose additional reported benefits are expected to be discovered as a result.</p>
<p>Villar, MV., 2013, Association between vitamin D and hepatitis C virus infection: A meta-analysis</p>	<p>Evaluation of the association between 25-hydroxy-D and SVR in HCV infected patients</p>	<p>IRR, level VII Variables: SVR, VD levels</p>	<p>Inclusion of 11 studies (eight observational and three interventional) with a total of n=1575 conducted by an academic facility in Brazil</p>	<p>VD serum measurements using radioimmunoassays and chemiluminescence. Viral load of HVC infection regardless of genotype</p>	<p>High rates of SVR were observed in HCV patients with VD >30ng/mL (OR 1.57; CI 95%) and those supplemented with VD (OR=4.59; 95% CI) of any genotypes</p>	<p>Clinical significance: higher SVR for those with higher VD levels or receiving supplementation. Supports VD supplementation. Limitations: some studies were small pop'n, lack of VD assessment in control and treatment groups, one study was not placebo controlled</p>
<p>Bitetto, D., (2011) Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis</p>	<p>Examine influence of vitamin D serum levels and/or vitamin D supplementation with respect to systemic virologic</p>	<p>Quantitative observational, cohort study. Level IV Variables: HCV quantitative serum, recurrence of SVR,</p>	<p>N=89 consecutive patients who underwent liver transplantation for HCV-related liver disease at a single academic center in</p>	<p>End of treatment viral response (undetectable level of HCV). Serum VD</p>	<p>Vitamin D status at the when patients started antiviral therapy was related to the SVR after treatment of recurrent HCV</p>	<p>Clinical significance: Supports VDS Limitations: Study design, retrospective study does not allow for complete control</p>

<p>C. Transplant International</p>	<p>response (SVR) rates for recurrent hepatitis C (RHC)</p>	<p>VD levels</p>	<p>Italy</p>		<p>Analyzing time to onset, evaluation of the relationship between vitamin D supplementation and resolution of HCV RNA and evidence of SVR was investigated</p>	<p>of confounding variables</p>
<p>VDS & Non-Alcoholic Fatty Liver Disease</p>						
<p>Eliades, M., 2015, <i>Vitamin D: A new player in non-alcoholic fatty liver disease?</i> World Journal of Gastroenterology</p>	<p>Examine the role of VDD in the development of NAFLD, review evidence that connects VDD and NAFLD demonstrate value of VDS</p>	<p>IRR, level VII Variables: VD levels, hepatic fibrosis, intestinal microbiome, insulin resistance</p>	<p>Not specified</p>	<p>Not specified</p>	<p>Evidence shows that VD could be useful in preventing the progression of NAFLD through various pathways such as anti-inflammatory and metabolic routes.</p>	<p>Clinical significance: supports VD supplementation Limitations: few prospective randomized studies examining of VD supplementation in NAFLD</p>
<p>Sharifi, N., (2014) <i>Does vitamin D improve liver enzymes, oxidative stress, and inflammatory biomarkers in adults with non-alcoholic fatty liver disease?</i> A randomized clinical trial. Endocrine</p>	<p>Determine the effect of VDS on serum liver enzymes, insulin resistance, oxidative stress, and inflammatory markers in NAFLD</p>	<p>Quantitative, experimental, RCT, double-blind, placebo controlled Level II Variables: VD levels, VDS, hs-CRP, MDA, LFT, HOMA-IR</p>	<p>N=53 patients with NAFLD, randomly allocated to receive VD or placebo every 2 wks for 4 mos in a single academic center in Iran</p>	<p>Wt, waist circumference, waist to hip ratio, BMI, dietary intake of VD, physical activity, ultrasound</p>	<p>Lab results of VD levels, VDS, hs-CRP, MDA, LFT, HOMA-IR, US</p>	<p>Clinical significance: supports VDS, shows benefit of VD in NAFLD and arresting progression to NASH Limitations: single-center study, smaller study size. US is not as diagnostic as liver biopsy for degree of steatosis</p>
<p>Iruzubieta, P., 2014, <i>Vitamin D deficiency in</i></p>	<p>Functions of VD involved in development of</p>	<p>Integrative review of research addressing VDD</p>	<p>Review of 23 articles (19 cohort, and 4 randomized</p>	<p>SVR, VD levels, HCV genotype, histology of liver</p>	<p>VD has pleiotropic effects that indicate a link between VDD</p>	<p>Clinical significance: VDS may improve</p>

<p>chronic liver disease World Journal of Hepatology</p>	<p>chronic liver disease (CLD) and relationship between VDD and two main causes of CLD: Hep C (HCV) and NAFLD</p>	<p>and supplementation in HCV cirrhosis and NAFLD. Level VII Variables: type of liver disease, VD levels and VDS, sustained virologic response (SVR) in HCV</p>	<p>prospective cohort studies) conducted by an academic facility in Spain.</p>		<p>and various chronic diseases (DM, CVD, AI, ID, several cancers and chronic disease). VD has been linked to increase risk of portal hypertension, mortality and worse histology in HCV and NAFLD.</p>	<p>complications listed from VDD as well as SVR after HCV treatment. Limitations: prospective randomized, placebo controlled studies are need to complete review</p>
<p>Vaidya, A., (2012) The independent association between 25-hydroxyvitamin D and adiponectin and its relation with BMI in two large cohorts: the NHS and the HPFS. Obesity</p>	<p>Evaluate the correlation between VD and adiponectin in large female cohort from the Nurses' Health Study I (NHS) and men from the Health Professional's Follow-Up Study (HPFS)</p>	<p>Quantitative, observational, in two large cohort studies Level IV Variables: VD and adiponectin levels, BMI</p>	<p>n=1206 for NHS n=439 for HPFS</p>	<p>Multivariable linear regression analyzed the independent link between 25(OH)D and adiponectin after adjusting for variables that would affect results</p>	<p>25(OH)D concentrations were correlated with high levels of adiponectin; independently related to adiponectin considering multivariable adjustments in both groups women: $\beta=0.06, P<0.001$; men: $\beta=0.07, P<0.05$</p>	<p>Clinical significance: supports VDS, reduced levels of 25(OH)D and adiponectin correlate with higher cardio and metabolic risk, evaluation of the effect of VDS on adiponectin is indicated Limitations: Cross-sectional study design cannot confirm causality, but findings were consistent with similar studies</p>
<p>Liangpunskal, S., (2011) Serum vitamin D concentrations and unexplained elevation in ALT among US adults. Digestive Diseases and Sciences</p>	<p>Analyze the association between serum vitamin D levels and elevated ALT of unknown etiology using the data from NHANESIII</p>	<p>Quantitative observational retrospective cohort study of NHANESIII conducted from 1988-1994 Variables: fasting glucose, LFTs, VD</p>	<p>n= 308 unexplained ALT elevation N=979 controls with normal VD</p>	<p>VD concentrations divided into fourths based on distribution and association was examined by multivariate logistic regression analysis</p>	<p>Participants with elevated ALT of unknown etiology had lower VD levels when compared to control group (61.8 ± 26.0 nmol/l vs. 66.8 ± 27.1 nmol/l, $P<0.01$)</p>	<p>Clinical significance: Negative correlation between elevated ALT and VD levels. Supports VDS Limitations: cross sectional design of the data does not</p>

		levels				show cause and effect relationship between serum vitamin D and unclear reason for elevation in ALT, results are from one measurement of serum vitamin D
Von Hurst, P., (2010) <i>Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient: a randomized, placebo-controlled trial</i> The British Journal of Nutrition	Examine the effect of optimized VD on markers of insulin resistance in South Asian women who were insulin resistant and VDD	Quantitative, randomized, double-blinded, placebo-controlled trial. Level II Variables: IR, VD levels, VDS	N=81 south Asian women with IR and VDD ages 23-68 residing in New Zealand	Serum D levels, IR	Notable improvements were observed in insulin sensitivity and resistance with VDS (P=0.003 and 0.02, respectively) IR most improved with VD of >80ng/mL. Lipid profile and hs-CRP were not affected by VDS	Improving VD status in IR women showed an improvement IR and sensitivity; insulin secretion unchanged. Ideal VD for reducing IR were shown to be 80 – 119 nmol/l, supports VDS. Limitations: compliance with regimen was lower after 3 mos, sun exposure may have affected VD levels versus PO VDS
VDS & Hepatic Osteodystrophy						
Chaney, A., 2015, <i>Effectiveness and outcomes of current practice in treating VDD in patients listed for liver transplantation</i> Endocrine Practice	Determine the effectiveness of one single-center's practice in addressing VDD in patients awaiting liver transplantation (LT)	Retrospective cohort study; Level IV Variables: MELD score, VD levels, bone mineral density (BMD), immunosuppression,	N=127 patients awaiting liver transplant in a single-center in Florida. Average MELD score=23 (lower value)	Serum VD levels, BMD via T-scores. No reliability reported	84% of patients had VDD. Only 62% received VD supplementation pre-LT. VDD improved with supplementation, no association found	Clinical significance: highlights lack of systematic supplementation. Limitations: Authors recognized their population's

		PTH level, BMI			between VDD at LT, functional status, fractures, or readmissions post-LT.	liver disease was not as advanced and therefore can maintain better VD levels at this point. Single center study.
Nakchbandi, I., 2014, <i>Osteoporosis and fractures in liver disease: Relevance, pathogenesis, and therapeutic implications</i> World Journal of Gastroenterology	Review discussing the relevance of bone loss in liver disease along with the evidence available describing the pathogenesis, diagnostic steps, and therapeutic options	IRR, level VII Variables: VD levels, fibronectin, insulin-like growth factor 1, various cytokines, corticosteroids	Literature review, studies not specified however bibliography numbered 137 manuscripts	Serum vitamin D levels	Liver disease is associated with compromises in bone health with a corresponding association of fracture risk in this population. A minimum of VD and calcium supplementation is recommended	Clinical significance: Supports VDS, reports an associated risk of fracture in liver failure. Limitations: focuses on the pathophysiology with limited actual studies supporting the theoretical disease process of bone loss and results of supplementation
Krol, C., 2014, <i>Longitudinal changes in BMD and fracture risk in orthotopic liver transplant recipients not using bone-modifying treatment</i> Journal of Bone and Mineral Research	Evaluate changes in BMD post OLT in liver transplanted patients not treated with antiresorptive agent to ID aspects of risk for loss of bone post OLT and study impact of changes in BMD on risk for fracture	Quantitative, observational, cohort, level IV Variables: OLT and BMD in femoral neck and vertebral and resulting or absence of fracture post transplantation	N=201 patients post OLT in a single center academic facility in The Netherlands	Changes in BMD via T-scores on DEXA scans	Significant relationship between age (>52y/o in women) OR 0.89, 95%CI and use of calcineurin inhibitors (CNI) for immunosuppression (IS) (OR 0.95;95% CI) VDD did not indicate bone loss either at lumbar spine (p=0.080) or femoral neck (p=0.674) Of risk factors evaluated, male gender (OR 5.15 95% CI) and age (OR 1.06; 95%	Clinical significance: After OLT, reversal of cholestasis, VDD, and hypogonadism, which results from improved liver function, likely contributes to improvement in LS BMD Limitations: lacked treatment protocol for IS therapy, excluded patients with bisphosphonate treatment not allowing for comparison of

					CI) were assoc w/increased risk of fracture	effects of treatments. Single center study.
Dasarathy, D., 2014 <i>Treatment to improve nutrition and functional capacity evaluation in liver transplant candidates</i> Current Treatment Options in Gastroenterology	Review of literature on Impact of malnutrition on liver transplant candidates	Integrative review of research, opinion statement, levels V and VII respectively. Variables: VDD, muscle mass, presence of sarcopenia, amino acid supplementation, micronutrient replacement	Not specified	Not specified	The data on VDS in improving outcomes could be stronger, however the material on poor outcomes in cirrhosis to VDD is credible. Replacing VD in cirrhotics should be standard of care in this population	Clinical significance: sarcopenia is an important complication of cirrhosis. One component that can help is VDS Limitations: lower level of evidence, but overall consistent with general consensus on VDS
Lucey, MR., 2013, <i>Long-term management of the successful adult liver transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation</i>	Clinical practice guidelines intended for providers treating adult liver transplanted patients suggesting select methods to diagnostic, therapeutic, and preventative facets of care	Clinical Practice Guideline by two expert organizations. Level VII	Guidelines based on: formal review and analysis of literature, a manual for assessing and designing practice guidelines, guideline policies, and the experience of the authors on the topic	VD serum levels, T-score values	Osteopenic LT recipients should perform regular weight-bearing exercises and receive calcium and VDS (grade 1, level A)	Clinical significance: supports VDS post OLT, something that could be carried on from pre-OLT status.
Holick, M., (2011) <i>Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline</i> The Journal of	Clinical guidelines for the evaluation, treatment, and prevention of VDD focusing on the care of patients who are at risk for deficiency	Clinical practice guidelines by expert organization. Level VII	Guidelines based on: systematic reviews of evidence and communication, discussion between members of the Endocrine Society	VD serum levels	Patients at risk for deficiency, such as CLD, should have a reliable VD level drawn and supplement if needed.	Clinical significance: supports VDS in high risk populations, including CLD, and post OLT due to nature of medications.

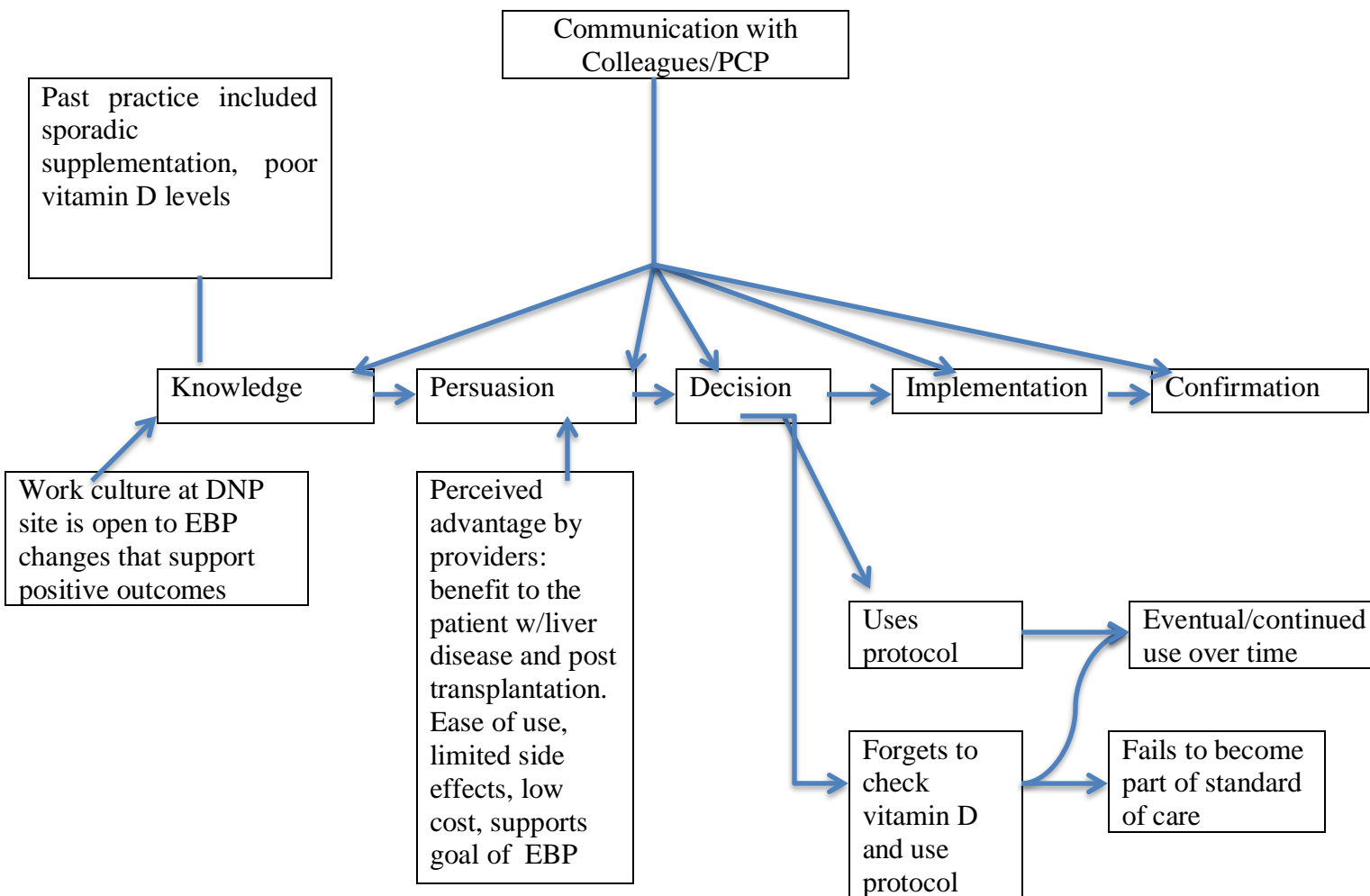
Endocrinology and Metabolism						
VDS & Mortality						
<p>Stokes, C., 2014, <i>Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis</i> European Journal of Clinical Investigation</p>	<p>Prospective exam of vitamin D levels in a cohort of adv. Liver cirrhosis, followed up for all-cause mortality</p>	<p>Quantitative, observational, prospective cohort, level IV Variables: vitamin d level, MELD, Child-Pugh scores,</p>	<p>N=65 patients with cirrhosis in a single-center academic facility in Germany</p>	<p>Serum 25-hydroxyvitamin D concentrations</p>	<p>High correlation between mortality and vitamin d levels in cirrhosis, 48% died over course of study. ROC analysis showed vitamin d level of 6ng/mL as minimum between survivors and non-survivors. Kaplan-Meier analysis of survival proved low vitamin d levels as predictor of death (OR=6.3, 95% CI, p=0.012)</p>	<p>Clinical significance: low vitamin d in pre-transplanted cirrhosis is a significant predictor of mortality. Supports VD supplementation. Limitations: single center study</p>
<p>Trépo, E., 2013, <i>Marked 25-hydroxyvitamin D deficiency is associated with poor prognosis in patients with alcoholic liver disease</i> Journal of Hepatology</p>	<p>Investigate the association of VDD with histological damage, portal hypertension, liver function, and mortality in alcoholic liver disease (ALD)</p>	<p>Quantitative, prospective case-control cohort study. Level IV Variables: serum VD levels in ALD patients and healthy controls, Child-Pugh scores</p>	<p>N=525 (n=324 caucasian ALD, n=201 healthy controls) at an academic facility in Belgium</p>	<p>Serum VD levels, peripheral blood mononuclear cells (PBMCs), tumor necrosis factor-alpha production</p>	<p>Low VD levels are associated with increased liver damage and mortality in ALD using univariate and multivariable logistic regression. Patient survival estimated by the Kalan-Meier method. Statistical analyses were performed using SPSS 19.0 software</p>	<p>Clinical significance: Data suggests that VDS could improve deleterious effects of pro-inflammatory cytokines in ALD. Supports supplementation</p>
<p>Thiem, U., 2013, <i>Calcidiol deficiency in end-stage organ</i></p>	<p>Review clarifying and summarizing existing data on the</p>	<p>Integrative Review of Research (IRR) of all solid organ</p>	<p>Inclusion of eight studies (one RCT, three retrospective</p>	<p>VD serum measurements, % of patients on VDS</p>	<p>Patients with liver failure are high risk for VDD.</p>	<p>Clinical significance: treatment with VDS</p>

<i>failure and after solid organ transplantation: status quo Nutrients</i>	average VDD in patients with organ failure and recipients of solid organ transplants. Also discusses interventional studies and clinical practice guidelines	transplantation systems and the effect of VD. Level VII Variables for OLT: VD levels, presence VD supplementation	cohorts, three prospective cohorts and one cross-sectional study) conducted by an academic facility in Austria		Supplementation is recommended by the Endocrine Society, the American Association for the study of liver disease, and the American Society of Transplantation	is recommended, especially in osteopenic liver transplant recipients with a Level of Evidence A. Limitations: Only one RCT represented.
Stokes, CS., 2013 <i>Vitamin D in chronic liver disease Liver International</i>	Discusses the epidemiological and functional relationships between VDD and CLD, as well as implications for therapeutic interventions	IRR, level VII Variables: serum level of VD, VDS, hepatic osteodystrophy	Inclusion of 15 studies evaluating the impact of VDS	Serum VD levels, BMD	VDD extremely common in CLD and inversely correlated with disease severity. Evidence is emerging in support of positive impact of VDS in SVR, and decreased acute cellular rejection post OLT	Clinical significance: Supports VDS, especially prior to OLT, as this may decrease incidence of ATCR post OLT Limitations: most of the studies reviewed are cross-sectional, sample sizes tended to be smaller
Zhao, G., (2012) <i>Serum 25-hydroxvitamin D levels and all-cause and cardiovascular disease mortality among US adults with hypertension: The NHANES linked mortality study.</i>	Whether concentrations of VD are inversely correlated with mortality risk among American adults with hypertension	Quantitative, retrospective cohort study Variables: VD, hypertension, all-cause mortality	N=2609 subjects with hypertension Data from the 2001-2004 National Health and Nutrition Examination Survey with mortality data obtained through 2006	Serum VD levels, presence of hypertension	Concentrations of VD as a continuous variable were linearly and inversely associated with the risk of mortality from all causes (P=0.012) and from CVD (P=0.010)	Clinical significance: although this study focuses on CVD population, it is telling with an all-cause mortality result
Autier, P., (2007) <i>Vitamin D supplementation and total mortality: A meta-analysis of</i>	Examine the risk of dying from any cause in subjects who participated in randomized trials testing the impact of VDS (ergocalciferol	Meta-analysis of RCTs Level I Variables: VD levels, VDS, any health condition	18 independent RCTs up to 2006 with a total of N=57,311	Serum VD levels, deaths from any cause, dose of VDS	Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship	Clinical significance: general support that VDS is beneficial to population.

<p><i>randomized controlled trials</i> Archives of Internal Medicine</p>	<p>[vitamin D(2)] or cholecalciferol [vitamin D(3)] on any health condition</p>				<p>between baseline VD status, dose of VDS, and total mortality rates remains to be investigated.</p>	
<p>VDS and Serum Response</p>						
<p>Jarett, F. et al., (2014) <i>The effective of oral supplementation of vitamin D3 on serum levels of vitamin D: A review.</i> Epidemiology</p>	<p>Examines the effect of vitamin D3 (dose-response) supplementation on serum level in 25 RCTs</p>	<p>Meta-analysis of RCTs Level I Variables: VD3 dosing, serum level response in health and ill individuals</p>	<p>25 RCTs examining VDS, 16 studies with healthy cohorts, 9 studies with disease and VDD</p>	<p>Serum VD levels, dose of VDS.</p>	<p>Positive correlation between amount of VDS and serum VD. p-value<0.001 and an r2 of 0.61.</p>	<p>Clinical significance: Supports VDS as a means to increase serum VD levels in both healthy and diseased populations</p>
<p>Pilz, S., Putz-Bankuti, C., Gaksch, M., Spindelboeck, W., Haselberger, M., Rainer, F., ... Stauber, R. (2016). <i>Effects of vitamin D supplementation on serum 25-hydroxyvitamin D concentrations in cirrhotic patients: A randomized controlled trial.</i> Nutrients, 8(278), 1-10</p>	<p>Examine the effect of VDS on patients with cirrhosis subsequently evaluating the changes in liver function and synthesis as a result of optimized vitamin D.</p>	<p>RCT: double blind, double center, placebo-controlled, parallel-group study Level II Variables: serum VD, liver function tests, international normalized ratio (INR), bilirubin</p>	<p>N=36 consecutive patients with cirrhosis randomized in to two groups, one received VD3 the control group, placebo, in two different academic centers in Austria</p>	<p>Serum VD levels, bilirubin, INR, LFT</p>	<p>Positive treatment effect as shown by increase in serum VD levels in cirrhotic patients, no changes between intervention and control group with respect to liver function</p>	<p>Clinical significance: Supports VDS as primary goal to increase serum VD</p>

Appendix D: Theory to Application Diagram

The Diffusion of Innovation Theory as applied to the DNP project:



Appendix E: Logic Model for DNP Project

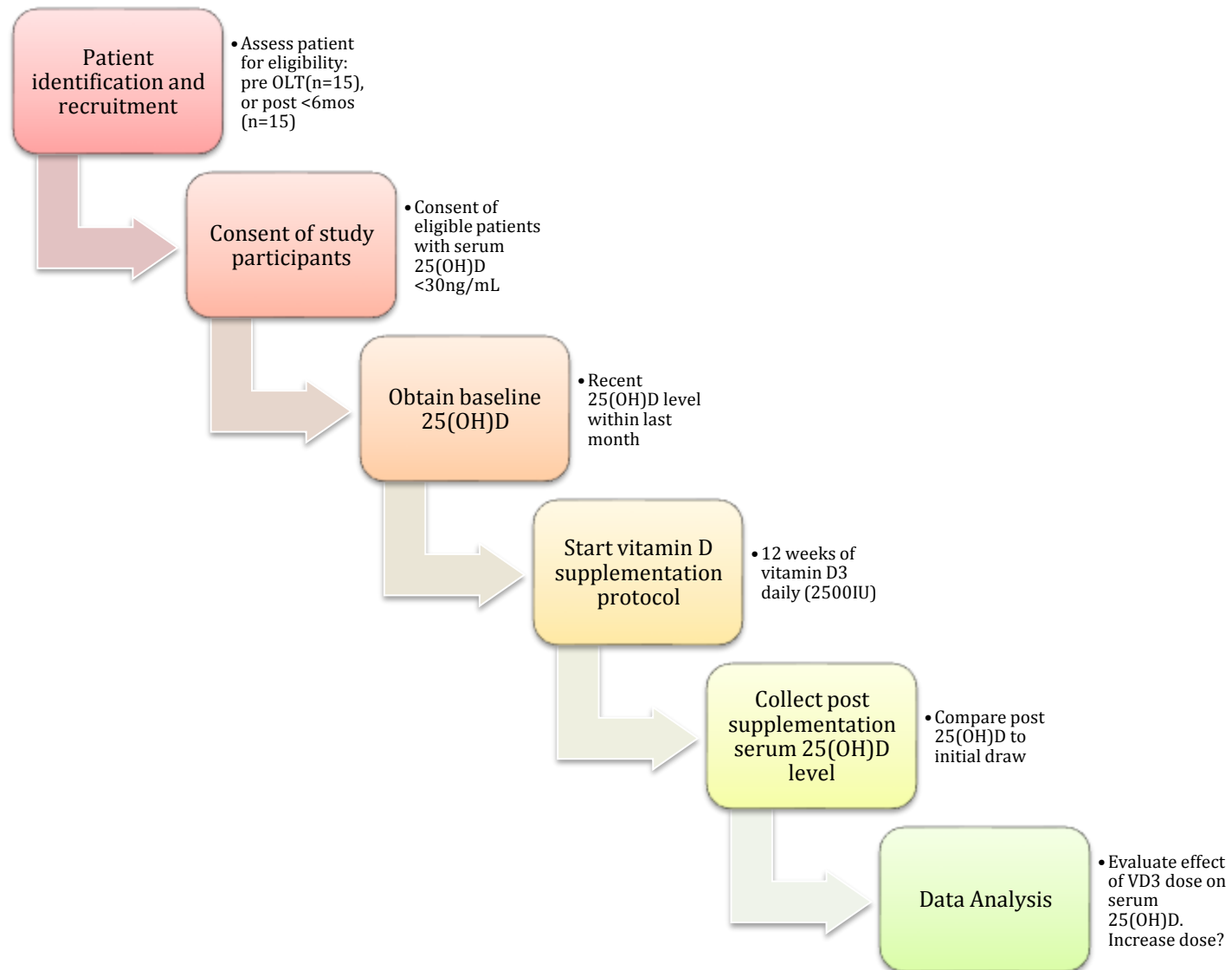
Adanted from Rogers (2003) DOI

Inputs	Intervention(s)		Outcomes -- Impact		
	Activities	Participation	Short	Medium	Long
<p>Evidence, sub-topics</p> <ul style="list-style-type: none"> • Vitamin D supplementation (VDS) and the immune system • VDS and Non-alcoholic fatty liver disease (NAFLD) • VDS and bone health • VDS and mortality • Clinical practice guidelines <p>Major Facilitators or Contributors</p> <ul style="list-style-type: none"> -DNP student -DNP Advisor -Inpatient nutritionist -Endocrine and Renal physicians -Outpatient nutritionist -Hepatologists -Fellow inpatient APRNs -Outpatient transplant coordinators <p>Major Barriers or Challenges</p> <ul style="list-style-type: none"> -Knowledge deficits of providers -Patient compliance 	<p>EBP intervention which is supported by the evidence in the Input column</p> <p>Improving serum vitamin D to clinical practice guidelines in liver disease to reduce impact of comorbidities in this population</p> <p>Major steps of the intervention</p> <ul style="list-style-type: none"> -Identification of patients that are severely deficient in vitamin D -Educate fellow providers on importance of VDS -Educate patients on the importance of compliance -Prescribe VDS protocol -Serial serum vitamin D checks over three months (monthly) 	<p>The subjects</p> <p>Patients with chronic liver disease listed for transplantation</p> <p>Site</p> <p>UCLA Medical Center</p> <p>Time Frame</p> <p><u>July 2016:</u> start inpatient provider education on VDS with presentation of DNP project, contact outpatient hepatologists at UCLA</p> <ul style="list-style-type: none"> -Identify intervention subjects via chart review <p><u>August:</u> Contact patients to educate on study, get consent</p> <p><u>September:</u> Start VDS on subjects with monthly checks through November</p> <p><u>December 2016:</u> Collect data, analyze</p> <p>Consent Needed or other</p> <ul style="list-style-type: none"> -IRB approval -Patient's consent <p>Person(s) collecting data</p> <ul style="list-style-type: none"> -Author of the DNP project -Nutritionist in clinic <p>Others: PCP, Hepatology</p>	<p>(Completed as student)</p> <p>Outcome(s) to be measured with valid & reliable tool(s)</p> <ul style="list-style-type: none"> -Serum vitamin D levels post VDS <p>Statistical analysis to be used</p> <ul style="list-style-type: none"> • One tailed t-test 	<p>(after student DNP)</p> <p>Outcomes to be measured</p> <ul style="list-style-type: none"> -Maintenance of vitamin D levels post VDS 	<p>(after student DNP)</p> <p>Outcomes that are potentials</p> <ul style="list-style-type: none"> -Incidence of bacterial infections -Incidence of acute cellular rejection in transplanted patients -Insulin needs in diabetic patients

Appendix F: DNP Project Timeline for vitamin D Supplementation in Liver Disease



Appendix G: Intervention Flow Diagram



Appendix H
Recruitment Script

We are conducting a study led by Cristin Grant, a nurse practitioner on the liver transplant service here at UCLA Medical Center. The subject of the study is the effect of a vitamin D3 protocol on our liver disease patient population.

We are looking at patients with low vitamin D. You were chosen because you have a history of liver disease, and your vitamin D level in your blood is low. We would like to see how you respond after a 12-week daily supplement of vitamin D3, which will be assessed through a blood sample after 12 weeks.

Liver disease severely affects the ability to process vitamin D, and this type of deficiency can contribute to many problems such as infection and poor bone health.

Your consent to participate in this observational study will allow the student researcher to view your lab results and decide if this form of vitamin D is effective at raising blood levels in chronic liver disease and transplanted patients.

If you chose not to participate, you will still receive vitamin D as needed.

Your participation is voluntary as well as confidential. The results will assist us in improving care for other patients like yourself, and your help is important to us.

Questions or concerns can be directed to the researcher, Cristin Grant, ACNP-BC at Cgrant@mednet.ucla.edu

Or, If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, please call the OHRPP at (310) 825-7122 or write to:

UCLA Office of the Human Research Protection Program
11000 Kinross Avenue, Suite 211, Box 951694
Los Angeles, CA 90095-1694

Appendix I IRB Approval Letter

NOTICE OF NEW APPROVAL

Principal Investigator: Lyla Lindholm
UMKC Health Sciences Building
Kansas City, MO 64108

Protocol Number: 16-333
Protocol Title: Vitamin D Supplementation in Liver Transplantation
Type of Review: M

Date of Approval: 07/27/2016
Date of Expiration: 12/31/2999

Dear Dr. Lindholm,

The above referenced study, and your participation as a principal investigator, was reviewed and approved by the UMKC IRB. You are granted permission to conduct your study as described in your application.

The above referenced study, and your participation as a principal investigator, was reviewed and determined to be Not Human Subjects Research (NHSR). As such, your activity falls outside the parameters of IRB review. You may conduct your study, without additional obligation to the IRB, as described in your application. The NHSR Determination is based upon the following Federally provided definitions:

"Research" is defined by these regulations as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

The regulations define a "Human Subject" as "a living individual about whom an investigator (whether professional or student) conducting research obtains: data through intervention or interaction with the individual, or identifiable private information."

All Human Subjects Research must be submitted to the IRB.

If your study changes in such a way that it becomes Human Subjects Research please contact the Research Compliance office immediately for the appropriate course of action.

This approval includes the following documents:

Attachments

The ability to conduct this study will expire on or before 12/31/2999 unless a request for continuing review is received and approved. If you intend to continue conduct of this study, it is your responsibility to provide a Continuing Review form prior to the expiration of approval.

This approval is issued under the University of Missouri - Kansas City's Federal Wide Assurance FWA00005427 with the Office for Human Research Protections(OHRP). If you have any questions regarding your obligations under the Board's Assurance, please do not hesitate to contact us.

There are 5 stipulations of approval:

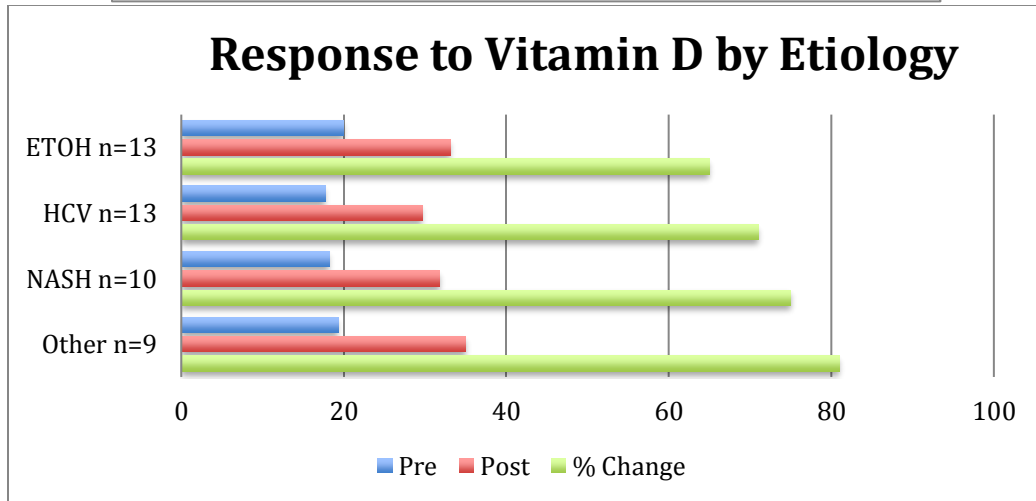
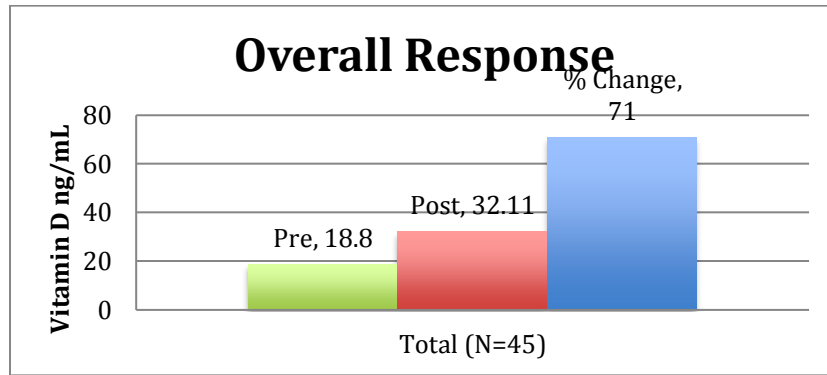
- 1) No subjects may be involved in any study procedure prior to the IRB approval date or after the expiration date. (PIs and sponsors are responsible for initiating Continuing Review proceedings).
- 2) All unanticipated or serious adverse events must be reported to the IRB.
- 3) All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk. This includes any change of investigator.
- 4) All protocol deviations must be reported to the IRB.
- 5) All recruitment materials and methods must be approved by the IRB prior to being used.

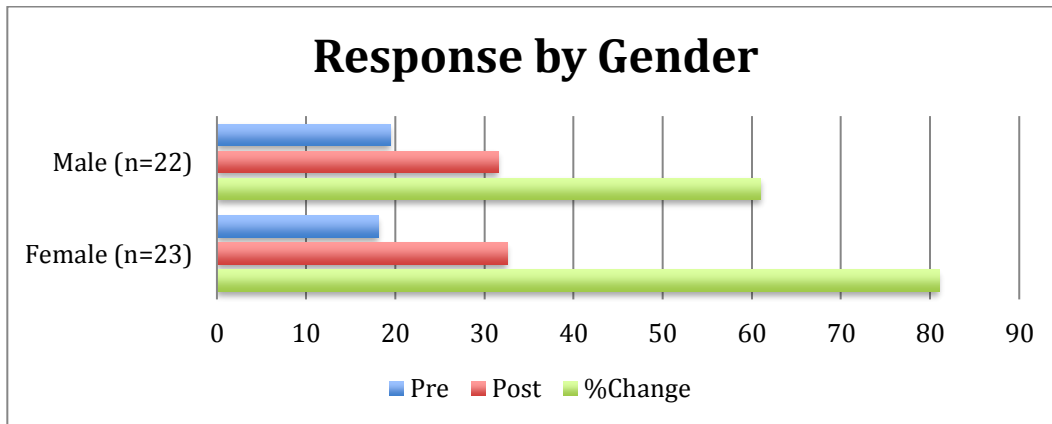
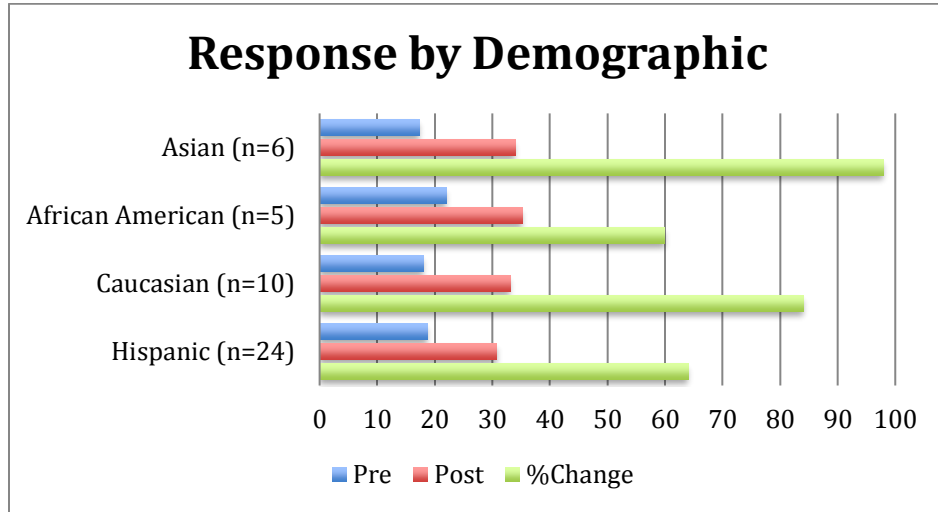
Please contact the Research Compliance Office (email: umkcirb@umkc.edu; phone: (816)235-5927) if you have questions or require further information.

Thank you,
Simon MacNeill
TEL: 816 235-5927
FAX: 816 235-5602

Appendix J
Example of Data and Results Tables

Patient ID	Age	Race	Gender	Etiology	Pre	Post	CHANGE
164	69	Hispanic	F	NASH	13	42	29
767	46	Hispanic	M	ETOH	21	21	0
159	68	Hispanic	M	ETOH	14	33	19
290	57	Afro-Amer	F	ETOH	23	29	6
189	61	Hispanic	M	HCV	27	37	10
160	57	Hispanic	F	ETOH	19	36	17
952	51	Caucasian	M	PSC	22	35	13
251	68	Asian	M	ETOH	12	47	35
876	69	Asian	M	HBV/HCV	26	35	11
430	58	Hispanic	M	HCV	22	28	6
280	28	Caucasian	F	NASH	18	24	6
749	68	Caucasian	F	HBV	22	36	14





Pre: level of vitamin D prior to protocol implementation

Post: Serum vitamin D redraw after 12 weeks of cholecalciferol

Appendix K
Statistical Analysis Table Template, Power Analysis

Power (95% Confidence Interval of observed proportion) by different sample sizes (n) and hypothesized proportions of patients who achieve normal vitamin D level after intervention (p), assuming we want to rule out the possibility that the proportion is 50%

	p=0.7	p=0.75	p=0.8	p=0.85	p=0.9
n=30	62% (0.54,0.86)	82% (0.6,0.9)	94% (0.66,0.94)	99% (0.72,0.98)	100% (0.79,1.01)
n=35	68% (0.55,0.85)	87% (0.61,0.89)	97% (0.67,0.93)	100% (0.73,0.97)	100% (0.8,1)
n=40	74% (0.56,0.84)	91% (0.62,0.88)	98% (0.68,0.92)	100% (0.74,0.96)	100% (0.81,0.99)
n=45	79% (0.57,0.83)	94% (0.62,0.88)	99% (0.68,0.92)	100% (0.75,0.95)	100% (0.81,0.99)
n=50	83% (0.57,0.83)	96% (0.63,0.87)	100% (0.69,0.91)	100% (0.75,0.95)	100% (0.82,0.98)
n=55	86% (0.58,0.82)	97% (0.64,0.86)	100% (0.69,0.91)	100% (0.76,0.94)	100% (0.82,0.98)
n=60	89% (0.58,0.82)	98% (0.64,0.86)	100% (0.7,0.9)	100% (0.76,0.94)	100% (0.82,0.98)
n=65	91% (0.59,0.81)	99% (0.64,0.86)	100% (0.7,0.9)	100% (0.76,0.94)	100% (0.83,0.97)
n=70	93% (0.59,0.81)	99% (0.65,0.85)	100% (0.71,0.89)	100% (0.77,0.93)	100% (0.83,0.97)
n=75	95% (0.6,0.8)	99% (0.65,0.85)	100% (0.71,0.89)	100% (0.77,0.93)	100% (0.83,0.97)
n=80	96% (0.6,0.8)	100% (0.66,0.84)	100% (0.71,0.89)	100% (0.77,0.93)	100% (0.83,0.97)

Calculations are based on the 'pwr' package in R according to the material by Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.).

This table assumes that we use a two-sided Z-test with normal approximation to make inferences about the proportion of a binary outcome, using $\alpha = 0.05$.

Power of hypothesis test using a proportion will be the approach to calculating power.

There is an expected proportion of 70-80% of subjects that will reach the minimum value of 30ng/mL of serum vitamin D.

UCLA Liver/Intestinal Vitamin D Protocol for Normal Renal Function and CKD 3 (approximate GFR >30)

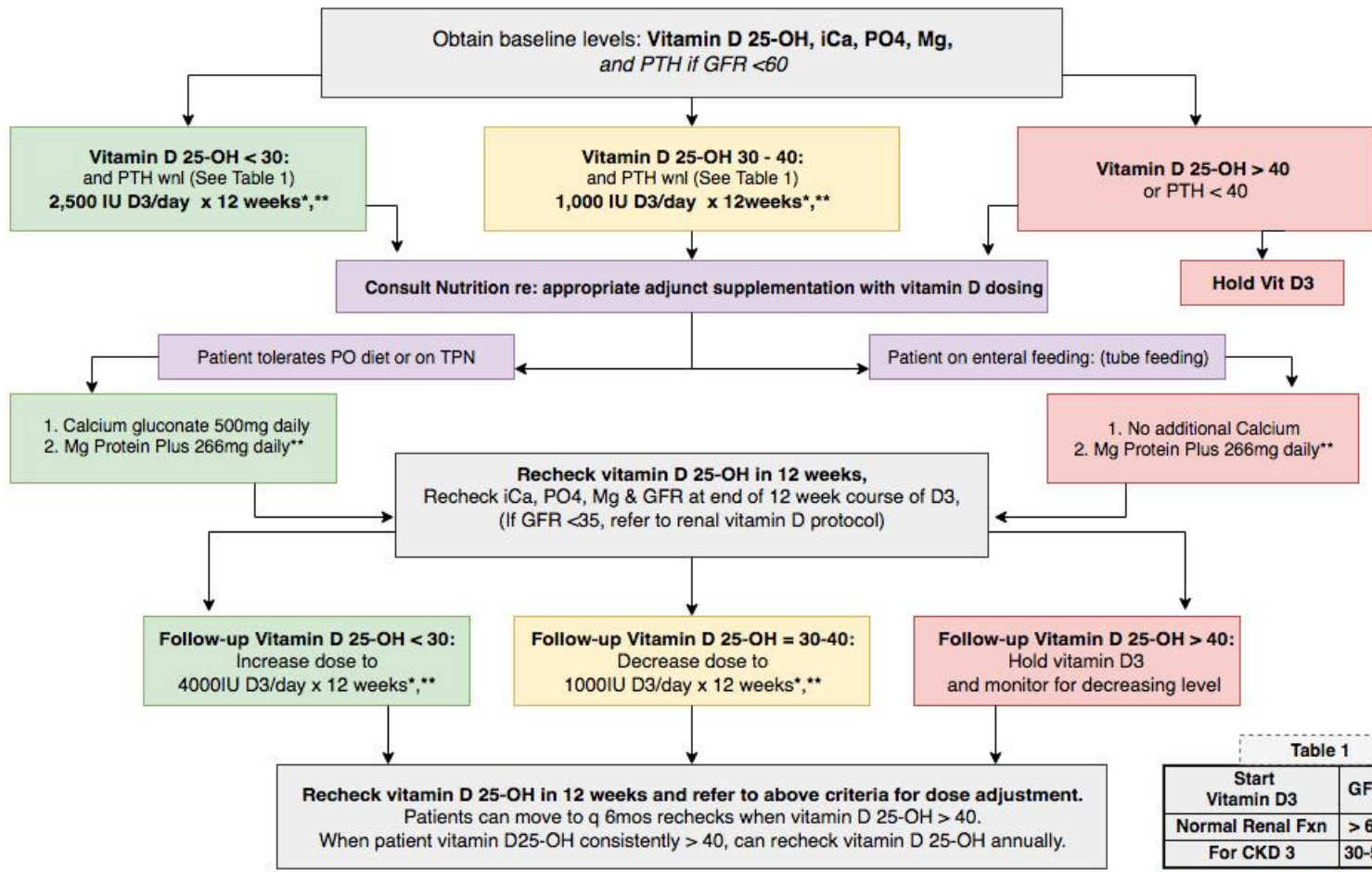


Table 1

Start Vitamin D3	GFR	Ideal PTH range
Normal Renal Fxn	> 60	WNL
For CKD 3	30-59	35-70

Note: Vit D supplementation suppresses PTH

Vitamin D3 (Vit D3) = Cholecalciferol

CONTRAINDICATIONS:
 *Hold vitamin D3 if iCa > 1.29/PO4 > 4.8 (IF PO4 ELEVATED, DISCUSS WITH RENAL RE: NON-CALCIUM BASED PHOSPHORUS BINDERS IF APPROPRIATE AND CALCIUM WNL)
 **Maintain Magnesium level 1.8-2.4 per ICU Mg protocol if NPO while inpatient (ALWAYS DEFER TO RENAL, AS Mg Supplementation MAY PUT PATIENTS AT RISK IF ON DIALYSIS)
 Note: contraindications for vitamin D supplementation include Williams disease, hypercalcemia, hyperphosphatemia, overly suppressed PTH (less than minimum goal per GFR & downtrending)



July 20, 2016

UMKC Institutional Review Board
University of Missouri-Kansas City
Kansas City, MO 64108

UMKC IRB,

This letter serves to provide documentation regarding Cristin Grant's Doctor of Nursing Practice (DNP) Project proposal. Ms. Grant obtained approval for her project proposal, A Vitamin D Protocol Post Liver Transplantation, from the School of Nursing DNP faculty committee on July 20, 2016.

If I can provide any further information, please feel free to contact me.

Sincerely,

A handwritten signature in black ink that reads "Susan J. Kimble". The signature is written in a cursive, flowing style.

Susan J. Kimble, DNP, RN, ANP-BC, FAANP
Clinical Associate Professor
DNP Programs Director
UMKC School of Nursing and Health Studies
816-235-5962

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