I, Emily A. Wolf, hereby submit this original work as part of the requirements for the degree of Master of Science in Nutrition.

It is entitled:
Assessing the Prevalence and Characteristics of Vitamin D Deficiency in Hemodialysis Patients in a Long Term Acute Care Hospital

Student's name: Emily A. Wolf

This work and its defense approved by:

Committee chair: Sarah Couch, PhD
Assessing the Prevalence and Characteristics of Vitamin D Deficiency in Patients on Hemodialysis in a Long Term Acute Care Hospital

A thesis submitted to the
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By

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ABSTRACT

Purpose: To assess the prevalence of vitamin D deficiency in patients on hemodialysis upon admission to a long term acute care hospital, as well as to examine characteristics of these individuals, with the purpose of identifying possible risk factors for vitamin D deficiency in kidney failure.

Subjects: 56 hemodialysis patients who were admitted on or began treatment with hemodialysis and were under the care of Dr. Patrick McCullough at the Drake Rehabilitation Center in Cincinnati, OH between June 2009 and December 2010 were included in this study.

Study Design and Methods: Data for this study were obtained as part of a retrospective observational cohort study of patients on hemodialysis who received vitamin D supplementation as standard of care while admitted to a LTACH. Patient data for this study were collected pre-supplementation at the baseline assessment visit. Biochemical data included 25(OH) D levels, 1, 25(OH)₂ D levels, Parathyroid hormone (PTH), serum calcium, and serum albumin. Demographic information and medical history were collected retrospectively from chart review. For analysis, patients were categorized into three groups based on widely used cutoffs for serum 25(OH) D in Chronic Kidney Disease; vitamin D sufficient (>30 ng/mL), vitamin D insufficient (<30 ng/mL but >10 ng/mL) and vitamin D deficient (<10 ng/mL). Differences were then explored between the groups for biochemical data, demographic information, and medical history.

Results: Seven percent (n=4) of the patients in the cohort were vitamin D sufficient, 48% (n=27) were vitamin D insufficient and 45% (n=25) were vitamin D deficient upon admission. No patients were diagnosed with a vitamin D deficiency prior to admission. As expected, vitamin D
supplementation upon admission was related to vitamin D group assignment with a greater number of sufficient patients being supplemented with vitamin D than in the other groups. The vitamin D deficient group was significantly younger than the vitamin D insufficient group. No differences were observed between vitamin D groups for mean serum calcium, albumin or PTH levels or number of individuals who had suboptimal levels of these analytes. The majority of patients in the cohort had suboptimal levels of both serum calcium and albumin. Notably, PTH levels met established targets in only 4 participants with suboptimal vitamin D status.

**Conclusion:** Based on these findings, the prevalence of vitamin D insufficiency and deficiency among patients with renal disease admitted to a LTACH is high, and vitamin D inadequacy is commonly undiagnosed in this at risk population. No specific demographic or clinical characteristics examined in this study were related to vitamin D deficiency grouping. The National Kidney Foundation’s guideline to assess 25 (OH) vitamin D in patients on dialysis if PTH levels exceed 300 pg/mL is likely to miss a significant number of individuals with suboptimal vitamin D status.

**Limitations:** It is difficult to determine risk factors for a specific condition (in this case vitamin D insufficiency) from a retrospective study. This study also had a small sample size and a limited number of patients in the vitamin D sufficient group, reducing the power of the study to detect group differences if they exist.
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LITERATURE REVIEW

I. Introduction

The widespread prevalence of vitamin D deficiency continues to be a highly controversial topic. While it is common knowledge that vitamin D deficiency is associated with bone related diseases such as rickets, osteomalacia and osteoporosis, the recent discovery that vitamin D also influences many genes with important physiological effects has made this an even greater publicized issue. Vitamin D deficiency has been linked to many different diseases, such as type 2 diabetes, cardiovascular disease and chronic kidney disease (CKD). As the kidneys are the main sites of vitamin D activation in the body, current research suggests that there may be a high prevalence of vitamin D deficiency in chronic kidney disease patients. The following literature review will describe the manner in which the body processes vitamin D and examine vitamin D assessment methods and approaches to supplementation. This review will also explain the pathophysiology of CKD and risk factors for developing this condition. Finally, this review will explain the connection between vitamin D deficiency and CKD, shedding light on why deficiency may be common among this population.

II. Digestion and Absorption of Vitamin D

While high levels of dietary vitamin D can be obtained through fish oils, it is very rare for the average adult to meet their Recommended Daily Allowance (RDA) for this nutrient through diet alone. Obtained most efficiently through solar ultraviolet B radiation, vitamin D is absorbed by the skin.\(^1\) Seven-dehydrocholesterol is converted to previtamin D3, which is then converted to vitamin D3 (also referred to as cholecalciferol). This process is universal to all animals- humans
also obtain vitamin D3 through meat consumption. Vitamin D2 (also referred to as ergocalciferol) is produced through irradiation of ergosterol, which is found in plants.\(^2\)

When coming from a dietary source, vitamin D3 is incorporated into chylomicrons, which are transported through the lymphatic and the venous circulation. D3 may also be stored in fat cells for later release. Vitamin D produced through sun exposure is circulated and stored in the same manner as D3. In the circulation, vitamin D from any source is bound to a vitamin D binding protein, which aids in its transport to the liver, where it is then converted to 25-hydroxy (OH) vitamin D by vitamin D 25-hydroxylase. Although inactive, 25(OH) vitamin D is the major circulating form of vitamin D and is very important in the assessment of an individual’s overall nutrient status for this vitamin. Upon transport to the kidney, 25(OH) vitamin D is converted to its active form, 1,25-dihydroxy (OH)\(_2\) vitamin D\(_3\).\(^{2-4}\) Recently, other activation sites for vitamin D have been identified, such as the prostate, colon, pancreas, lymphocytes and breast.\(^3^4\) The conversion and production of 1,25(OH)\(_2\) vitamin D in the kidney is regulated by plasma levels of parathyroid hormone (PTH) as well as serum levels of calcium and phosphate, and an inverse relationship between PTH levels and circulating vitamin D has been proven.\(^5^6\) High levels of active vitamin D promote the absorption of intestinal calcium and phosphorous.\(^2^6\)

**III. Assessing Vitamin D Status**

Much attention has been paid to vitamin D deficiency due to its growing prevalence in the United States. Diseases such as rickets, osteomalacia and osteoporosis are associated with vitamin D deficiency, the cause being related to impairment in calcium absorption resulting from a deficiency in vitamin D.\(^7\) More recently, the relationship between vitamin D and non-skeletal
diseases such as type 1 diabetes, chronic kidney disease and certain types of cancer is being explored. Empirical evidence now suggests that supplementation with vitamin D in early infancy can reduce a child’s chance of developing type 1 diabetes. Studies have also found a connection between vitamin D deficiency and other autoimmune diseases such as asthma, multiple sclerosis and inflammatory bowel disease. Recent findings also imply that low levels of serum vitamin D are linked to hypertension and an increase in deaths related to cardiovascular diseases (CVD), while vitamin D adequacy has been related to lower mortality rates in cancer patients. At different times during the year, the prevalence of vitamin D deficiency in the U.S. is estimated to be between 40-90%, with an estimated 1 billion people worldwide at risk of developing the condition. Furthermore, NHANES III showed that African-Americans and individuals of Hispanic ethnicity are most commonly deficient, as well as obese individuals. In addition to this, vitamin D deficiency is more prevalent in the older adult population compared to younger age groups.

Presently, the most accurate way to assess vitamin D status is by testing levels of serum 25(OH) vitamin D, with liquid chromatography- mass spectrometry as the “gold standard” of assays. A serum 25(OH) vitamin D concentration of 50 nmol/L (20 ng/mL) or higher has been identified as optimal by the Institute of Medicine of the United States National Academy of Sciences. This level has been documented to be the point at which maximum calcium absorption takes place, with increased risk of developing rickets and other bone-related diseases at 25(OH) vitamin D levels below this cutoff. No added health benefits have been proven at levels above this cut-off. Furthermore, serum 25(OH) vitamin D levels of 30-50 nmol/L (12-20 ng/mL) are considered inadequate while levels below 30 nmol/L (or 12 ng/mL) are considered to be a severe vitamin D deficiency. It is important to keep in mind that these
cutoffs refer to healthy individuals. In diseased states, different cutoffs may apply. For example, the National Kidney Foundation states that serum 25(OH) vitamin D levels below 30 ng/mL are considered insufficient, as these levels are associated with secondary hyperparathyroidism as well as reduced bone mineral density in individuals with CKD.21 The current RDA for vitamin D is 600 IU for individuals between the ages of 1-70 years and 800 IU for adults 71 years of age and older. The RDA for vitamin D is based on empirical evidence indicating that this dietary amount is sufficient to achieve a serum 25(OH) vitamin D level above 50 nmol/L.18

IV. Vitamin D Supplementation

As mentioned previously, there are two forms of vitamin D: D2 and D3. Cholecalciferol (D3) is generated by the conversion of 7-dehydrocholesterol when skin absorbs sunlight. Ergocalciferol (D2) is generated by the UV irradiation of ergosterol in yeast. The only chemical difference between these two forms of vitamin D is a difference in the structure of their side chain.22 While there have been many debates about which form is more “potent” (e.g. increasing 25(OH) vitamin D levels), no definitive conclusion has been reached.

Studies dating back as far as 1982 have claimed that large doses of vitamin D3 are more effective at raising serum 25(OH) vitamin D levels than D2. From early experimental trials in animals, D3 was found to be more effective in raising levels of serum 25(OH) vitamin D than D2.23 Over the years, the same type of relationship has been cited in many human studies. The most recent of these studies was conducted by Heaney et al, which compared the potency between vitamin D2 and D3 in a single blind randomized study of 33 adults. The groups were supplemented with either D2 or D3, at a dosage of 50,000 IU/week over a 12 week period.
Serum 25(OH) vitamin D was measured in two week increments along with fat samples tested for vitamin D content. Results showed that D3 was 56-87% more effective at raising 25(OH) D levels and three times as effective at raising calciferol content in fat than D2.23 While these findings are statistically significant, there are several studies showing the opposite effect, making it impossible to come to a definitive conclusion.24 At present, one can conclude that both forms of vitamin D have the ability to effectively raise 25(OH) vitamin D serum levels and cure rickets.

V. Health Benefits Associated with Vitamin D

The importance of achieving optimal levels of serum 25(OH) vitamin D is made apparent through understanding its influence on bone health as well as many other important processes in the body. Vitamin D plays an important role in bone health as it regulates calcium in the body, with the help of PTH. When the parathyroid gland senses low serum calcium, PTH synthesis and secretion is increased. While PTH has a direct effect on the bone, contributing to calcium and phosphorous release into the blood, the hormone also activates the enzyme that converts 25(OH) vitamin D to its active form - 1,25(OH)2 vitamin D. The active form of vitamin D works to increase calcium absorption in the small intestine as well as renal reabsorption of calcium in the kidneys. With a vitamin D deficiency however, this latter step cannot take place. Although PTH mobilizes calcium from the bone to replenish serum levels, vitamin D inadequacy results in inadequate levels of blood calcium necessary for proper bone health.18 From this, diseases such as rickets, osteomalacia or osteoporosis may occur.

The health benefits of vitamin D stretch far beyond calcium related diseases. The recent discovery that vitamin D influences a large number of genes lends support for the notion that
vitamin D may impact many different diseases, as these genes regulate important processes such as cell proliferation, maturation and apoptosis, among many other functions.\textsuperscript{25,26} For example, the fact that genes influenced by vitamin D have the ability to inhibit cancer cell proliferation is the basis for many studies that have examined a possible role of vitamin D in reducing cancer mortality.\textsuperscript{12-14}

Vitamin D sufficiency has been cited as a common defense against many other diseases as well. While vitamin D deficiency is commonly seen in patients with Crohn’s Disease, there has also been a strong relationship observed between 25(OH) vitamin D levels and other autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis.\textsuperscript{9,10,27} Vitamin D may also help to decrease renin production and enhance insulin production, both important processes in regards to hypertension and type 2 diabetes mellitus, respectively. Maintaining a sufficient level of vitamin D may therefore positively impact blood pressure and pancreatic function and prevent hypertension and type 2 diabetes.\textsuperscript{28} Genes influenced by vitamin D also play a role in decreasing inflammatory markers commonly found in patients with cardiovascular disease.\textsuperscript{11}

\textit{VI. Conditions that Impair the Absorption and Metabolism of Vitamin D}

While old age and insufficient sun exposure are risk factors for developing a vitamin D deficiency, diseases that impair vitamin D absorption may increase risk as well. For example, many people suffering from inflammatory bowel and liver disease may be vitamin D deficient due to issues of vitamin D malabsorption. Patients with liver disease are also at risk for developing vitamin D deficiency due to the fact that the liver is the site of vitamin D hydroxylation to its semi-active form. The liver is also the site of vitamin D binding protein
This binding protein plays an important role in transporting vitamin D in the circulation as well as promoting its uptake by other tissues. CKD is perhaps the most widely studied condition in which vitamin D metabolism and absorption is impaired. A commonly held viewpoint among the medical community is that without functioning kidneys, 1,25(OH)$_2$D$_3$, the active form of vitamin D cannot be synthesized. Whether or not this viewpoint is substantiated by empirical evidence will be discussed below.

VII. Chronic Kidney Disease- Pathophysiology

CKD, as defined by the National Kidney Foundation, refers to damage to the kidneys resulting in a glomerular filtration rate (GFR) of less than 60 mL per minute per 1.73m$^2$ for a period longer than three months. The development of CKD may be attributable to many different conditions, such as type 2 diabetes, hypertension and cardiovascular disease. While in some patients, kidney function deteriorates quickly, other cases may progress slowly. CKD is characterized by a decline in the GFR, resulting in an excessive buildup of urea and other nitrogenous wastes in the blood stream. An impairment in the kidney’s ability to filter out waste will result in higher levels of blood urea nitrogen (BUN) and a low creatinine clearance, which can both be early identifiers of the disease. Decreased renal function can also result in hypertension, as the kidney plays an important role in maintaining blood pressure.

CKD is commonly characterized by five stages. As each stage progresses, the glomeruli become increasingly damaged and result in a decrease in filtration rate, resulting in excessive protein loss from the kidneys along with high levels of creatinine and waste in the blood. Symptoms and complications progress as well, such as high blood pressure, anemia, uremic
breath and neuropathy in the extremities. Once the disease has progressed to stage 5, also known as end stage renal disease, the kidney becomes completely non-functional.\textsuperscript{30}

\textit{VIII. The Population Impacted by Chronic Kidney Disease}

Risk for CKD does not appear to be related to any particular population group, however the comorbidities associated with obesity increase a person’s risk of developing the disease. The development of CKD is also linked to people with hyperlipidemia, hypertension, CVD and diabetes mellitus.\textsuperscript{30} An example of this relationship is the Pima Indians of Arizona, a group of Native Americans known for their high incidence of obesity, diabetes mellitus and CKD. In examining a group of 5056 Pima Indians from 1975-1986, researchers observed 80 incident cases of end stage renal disease with all but 2 of the cases attributable to type 2 diabetes mellitus. Also significant was the observation that incidence of CKD increased with hypertension.\textsuperscript{31} Similar studies have been conducted with the Zuni Indians of the United States as well as the Australian aborigines of the Tiwi Islands.\textsuperscript{32,33}

The idea that CKD is prevalent in the global older adult population is not surprising to most. Seven percent of the world’s population is over 65 years of age and the prevalence of obesity is greater than 30\% in American middle-age and older adults. Obesity related diseases such as type 2 diabetes, hypertension and cardiovascular CVD help to make this population very susceptible to CKD.\textsuperscript{34} Data taken from NHANES III revealed that 46\% of study participants age 70 and older had CKD. International data also showed this as a trend, particularly in countries such as China and Japan.\textsuperscript{35-37}
The Treatment of Chronic Kidney Disease

As CKD progresses, the effects of the disease on all organ systems of the body can be devastating. This makes early detection and treatment of this disease critical in order to halt its progression before reaching the end stage in which the kidney is unable to function. Since hypertension, CVD and diabetes mellitus are closely related to the development of CKD, an important part of treating early stages of the disease include managing these co-morbidities. Guidelines on treating associated comorbidities are provided by the Kidney Disease Outcomes and Quality Initiative (KDOQI). These guidelines suggest that keeping tight regulation of blood pressure in patients with CKD helps to slow the progression of kidney damage and recommend that the use ACE inhibitors and angiotensin-II receptor antagonists are ideal treatments for lowering intra-glomerular pressure and decreasing amounts of protein lost in the urine from patients with CKD. The guidelines note that with diabetes mellitus as such a common risk factor for developing nephropathy, the progression of CKD can be slowed drastically by maintaining good glycemic control by keeping hemoglobin A1C under 7%. The KDOQI guidelines also suggest that it is important to control lipid levels in the blood, as dyslipidemia is a major complication of CKD and may play a role in decreasing kidney function. In these cases, statins have been effective at reducing LDL cholesterol and risk of CKD. Needless to say, lifestyle modifications such as consuming a healthy diet and participating in regular exercise may help to minimize the occurrence of co-morbidities so that progression of the disease may be halted.

Once CKD progresses, the patient may need to be put on dialysis and possibly receive a transplant, referred to as renal replacement therapy. While certain patients will undergo dialysis for a short period of time and then receive a new kidney, others may be on dialysis for the rest of their lives. The role of dialysis is to perform the function that the failed kidney is unable to; it
prevents buildup of wastes in the blood, keeps control over blood pressure and ensures that the patient’s body retains the substances it needs, such as electrolytes. Patients may either undergo hemodialysis or peritoneal dialysis. Hemodialysis, which cleans (e.g., filters and removed impurities) a patient’s blood by way of an artificial kidney, is most commonly performed in dialysis centers. When being treated with peritoneal dialysis, a patient’s blood is cleaned within their body.\(^3\) While many studies have cited much larger mortality rates for patients undergoing peritoneal dialysis, limitations of these studies make them inconclusive.\(^4\)

It is important to note that nutritional requirements change when CKD is treated with dialysis. This is due to the fact that patients generally lose protein, glucose, amino acids, water soluble vitamins and other nutrients when undergoing dialysis. Patients may also be consuming a diet of poor nutritional quality due to illness and related stress. With this in mind, it is recommended that patients meet with a dietitian at their dialysis center to tailor a food plan that will help them reach their calorie and nutrient needs. In general, the National Kidney Foundation recommends patients’ daily caloric intake should be between 30 to 35 calories per kilogram of body weight per day. The National Kidney Foundation also recommends that patients on dialysis consume no less than 1.2 grams of protein per kilogram of body weight per day.\(^4\) Checking a patients’ serum levels for certain nutrients after dialysis may be helpful when determining if a certain patient’s nutritional needs are being met. For example, if a blood panel shows that albumin levels are low, this may be indicative of an increase in protein loss in the dialysate, and it may be necessary to increase the patient’s daily protein intake.\(^4\)
XI. The Connection Between Vitamin D and Chronic Kidney Disease

As previously discussed, CKD is characterized by an increasing impairment of renal function. As many studies have noted, as GFR decreases, $1,25(OH)_2$ vitamin D levels decrease as well. In later stages of the disease, the conversion of $25(OH)$ vitamin D to $1,25(OH)_2$ vitamin D which takes place in the kidney is impaired. This occurs because $25(OH)$ vitamin D-1a-hydroxylase, the enzyme that is responsible for the transformation of vitamin D to the active form is regulated by PTH and low phosphate levels. The kidney’s inability to properly excrete phosphate results in hyperphosphatemia, inhibiting the enzyme’s activity. Proteinuria resulting from CKD can also result in impaired reabsorption of vitamin D in the nephron and large amounts of $25(OH)$ vitamin D bound to vitamin D binding protein have been documented in the urine of CKD patients.

XI. Prevalence of Suboptimal Vitamin D Status in CKD Patients

Vitamin D insufficiency is most commonly observed in stages 3, 4 and 5 of CKD patients. A retrospective study of patients at five different hemodialysis centers in western Massachusetts assessed the prevalence of serum $25(OH)$ vitamin D levels below 40 ng/mL as well as 31 ng/mL. Results showed that 90% of the patients had serum levels below 40 ng/mL with 80% below 31 ng/mL. Data collected by NHANESIII has also been analyzed showing that CKD patients are at a much higher risk of suboptimal $25(OH)$ vitamin D levels compared to those without the disease, despite no difference in dietary vitamin D. Further analysis showed that the odds ratio (OR) for patients with CKD of having a serum $25(OH)$ D level of 15 ng/mL-30 ng/L was 1.15 (95% CI, 0.92-1.44) and the OR of having a $25(OH)$ D level of <15 ng/mL was 1.39 (95% CI,
Evidence from other studies also show that suboptimal vitamin D seemed to be an even bigger problem for CKD patients than for the general population.35

XII. Current Vitamin D Recommendations for CKD Patients

Currently, the National Kidney Foundation offers clinical practice guidelines for the treatment and management of CKD patients with vitamin D supplementation. The guidelines suggest that serum 25(OH) vitamin D be tested in any patient with a PTH level above the target range for their stage of chronic kidney disease. For end stage renal disease, this range is 150-300 pg/mL. Once 25(OH) vitamin D levels are tested, the National Kidney Foundation suggests that patients with levels of 30 ng/mL and below receive vitamin D supplementation in low doses of the active sterol, calcitriol. Evidence has shown that calcitriol is most effective at lowering serum PTH, and hyperparathyroidism is commonly associated with both low vitamin D and CKD. Furthermore, studies have shown supplementation with .25 ug -.5 ug of active vitamin D per day can lower PTH levels without demonstrating any renal harm.21

XIII. Health Benefits of Vitamin D Supplementation for CKD Patients

Vitamin D supplementation is very important for the CKD patient, given their lack of ability to produce 1,25(OH)2D in the kidneys.4 While vitamin D supplementation has an obvious effect on mineral metabolism, it has many benefits far beyond this. Research provides evidence that vitamin D deficiency further complicates the damage done by CKD, citing that low levels are
often associated with increased mortality in CKD patients.\textsuperscript{35,47} Evidence from recent studies show that supplementation in the form active vitamin D and its analogues can effectively raise serum 25(OH)D levels and may benefit the chronic kidney disease patient by reducing cardiovascular related mortality, improving glycemic control as well as decreasing inflammatory markers.\textsuperscript{4,11,48}

Stubbs et al questioned whether nutritional supplementation of vitamin D has a positive effect on patients with end stage renal disease, finding that when given cholecalciferol, patients were able to achieve “normal” levels of 1,25(OH)\textsubscript{2}D as well as decrease inflammatory cytokine levels.\textsuperscript{49} Kovesdy et al sought to explore whether supplementation with oral calcitriol would decrease incidence rate of mortality and dialysis in chronic kidney disease patients not yet on dialysis. After supplementing 258 out of 520 patients in stages 3-5, researchers found that the incidence rate for both were much lower in those receiving vitamin D treatment vs. those who were untreated.\textsuperscript{50} While much evidence supports the idea that chronic kidney disease patients can benefit from vitamin D supplementation, further research is necessary to answer the question of what forms are best and at what dosage.

\textit{XIV. Rationale for Current Study and Purpose}

As evident by the studies previously discussed, vitamin D deficiency is a widespread problem for CKD patients. However there is limited data regarding the specific risk factors associated with vitamin D deficiency in hemodialysis patients. The overall goal of the current study was to explore vitamin D deficiency in patients receiving hemodialysis in a long term
acute care hospital (LTACH) and identify the patient characteristics and clinical factors associated with insufficient levels of vitamin D.

METHODS

Subjects

The study sample consisted of 56 patients with temporary renal failure or end stage renal disease (ESRD) who were admitted to the Drake Rehabilitation Center, a LTACH in Cincinnati, Ohio from June 2009 to December 2010. Patients were included in this study if they were being treated with hemodialysis for renal failure either on a temporary or chronic basis and were placed under the care of Dr. Patrick McCullough, the primary internist who treats all dialysis patients at the Drake Rehabilitation Center. All hemodialysis patients seen at the Drake Center from June 2009-December 2010 were included in this study, with no exclusions. Forty-two of the patients in this study were ESRD patients and remained on hemodialysis upon discharge from the Drake Center; this group of patients was classified as chronic dialysis patients. The remaining 14 patients suffered from acute kidney damage and were classified as temporary dialysis patients.

Research Design

The data included in these analyses were baseline values from a retrospective observational cohort study of patients on hemodialysis who received vitamin D supplementation as standard of care while admitted to a LTACH. The retrospective data collection protocol for this study was approved by the Drake Rehabilitation Center Institutional Review Board. Baseline (pre-supplementation) biochemical data retrieved from medical charts were those reflective of lab
values collected within 24 hours after admission. and included serum 25(OH) vitamin D, serum 1,25(OH)_2 vitamin D, serum calcium, serum parathyroid hormone and serum albumin. Demographic characteristics retrieved from medical charts included age, race/ethnicity, gender and medical history data included vitamin supplementation frequency and dosage and major medical diagnoses.

**Biochemical Assessment**

All clinical laboratory data retrieved for patients in this study were those obtain upon admission (e.g., considered initial or baseline levels in this cohort) and were measured in the clinical laboratory at the Drake Hospital Rehabilitation Center.

**Vitamin D Labs:** Patients’ serum 25(OH) vitamin D and 1,25(OH)_2 vitamin D were measured by radioimmunoassay. Values of 30–100 ng/mL were considered normal; 10–30 ng/mL were considered insufficient and <10 ng/mL were considered severely deficient based on the KDOQI guidelines and widely used cutoffs.\(^5\)

**Serum calcium:** Patients’ calcium was measured using both the cresolphthalein complexone method and arsenazo III dye. Values of 8.9–10.4 mg/dL were considered normal.

**Serum albumin:** Patients’ albumin was measured upon admission using either the bromocresol purple or green dye binding method. Values of 3.5–5.1 g/dL were considered normal.

**Parathyroid hormone:** The Drake Center laboratory took a direct measurement of PTH upon each patient’s admission. The lab defined normal values for PTH as 7.5–53.5 pg/mL, however this study also considered PTH targets for patients with ESRD from the National Kidney Foundation\(^2\) which were 150–300 pg/mL.
Medical history data and demographic information retrieved:

Supplement use: Each patient’s vitamin supplement frequency of use was recorded at the time of admission. Dr. McCullough took note of whether each patient was on a vitamin D supplement prior to admission, as well as whether each patient was taking a multivitamin. This information was obtained from the patients’ lists of medications upon admission to the Drake Center.

Diagnosed vitamin D deficiency: Dr. McCullough took note of whether each patient was admitted to the Drake Center with a diagnosis of vitamin D deficiency. If a deficiency was not listed in a patient’s medical history upon admission, the patient was considered to be undiagnosed.

Demographics – The patient’s age, sex and race were collected retrospectively off of the Drake Center’s medical records for each participant.

Diagnosis – Patients’ major diagnoses besides ESRD were collected retrospectively from admission notes, obtained from the Drake Center’s medical records for each patient.

Data analysis

For analysis, patients were categorized into 3 different groups according to serum vitamin D concentrations. Groups were defined according to the Kidney Disease Outcomes and Quality Initiative guidelines as well as widely used cutoffs for vitamin D status, with group 1 considered “vitamin D sufficient” at 30 ng/mL or greater, group 2 considered “vitamin D insufficient” at levels between 10-29 ng/mL and group 3 considered “vitamin D deficient” at serum levels below 10 ng/mL. Differences in biochemical data and demographic and clinical characteristics were then explored between the three groups.
Statistics were calculated using the Statistical Analysis System for Windows (SAS, version 9.2). For continuous variables, means and standard deviations were calculated and for categorical data, frequencies were derived. Differences were then examined between the vitamin D deficiency groups using the Fisher’s exact test for comparison of proportions for categorical data and the general linear model procedure (the one way ANOVA) for continuous data. The Tukey method post-hoc test was run for significant GLM findings. P values <.05 were considered significantly different.

RESULTS

Patient Characteristics

Out of the 56 patients studied, 7% were vitamin D sufficient, while 48% were vitamin D insufficient and 45% were vitamin D deficient. The frequency distribution of 25(OH) vitamin D levels can be seen in Figure 1. Characteristics of the 25(OH) vitamin D groups can be found in Table 1. Patients ranged in age from 26-87 years, with patients in group 2 being significantly older than those in group 3 \((p<.05)\). No significant differences were observed between the 3 groups for gender, race, or duration of dialysis (chronic vs. temporary dialysis).

Vitamin D Deficiency and Supplementation Prior to Admission to the LTACH

No patients were diagnosed with a vitamin D deficiency prior to admission (Table 1). As expected, vitamin D supplementation upon admission was related to vitamin D group assignment
with a greater number of the sufficient patients being supplemented with vitamin D compared to the other groups ($p<.05$).

*Biochemical Labs*

There were no significant differences between the three vitamin D sufficiency groups for serum calcium, PTH or albumin levels or number of individuals who had suboptimal levels of these analytes (Table 1). Serum calcium and albumin levels were below normal range for the majority of patients. Notably, PTH levels met established National Kidney foundation targets in all but 4 patients with suboptimal vitamin D status.

Table 1 shows each group’s serum 25(OH) vitamin D and 1,25(OH)$_2$ vitamin D at their time of admission. Group 1 showed an average 25(OH)D of 42.5 ng/mL while groups 2 and 3 averaged 16.2 and 7.1 ng/mL, respectively. As expected, (and confirming group assignment), a significant difference in mean 25(OH) vitamin D was observed between each group ($p<.05$). For 1,25(OH)$_2$D, group 1 averaged 25.1 ng/mL while group 2 and group 3 averaged 15.6 and 10.5 ng/mL, respectively. The serum 1,25(OH)$_2$ vitamin D levels of group 1 were significantly higher than group 3’s ($p<.05$).
Figure 1. Frequency distribution of serum 25(OH) vitamin D levels in Hemodialysis patients in a long term acute care hospital

![Frequency distribution graph]

Table 1. Data** Comparison between levels of 25(OH) D deficiency

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Sufficient (n=4)</th>
<th>Group 2 Insufficient (n=27)</th>
<th>Group 3 Deficient (n=25)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
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<td>71.3 ± 4.1&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>65.6 ± 13.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55.8 ± 14.7&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Gender</td>
<td></td>
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<tr>
<td>Female</td>
<td>1 (25)</td>
<td>12 (46)</td>
<td>8 (33)</td>
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<tr>
<td>Male</td>
<td>3 (75)</td>
<td>15 (54)</td>
<td>17 (67)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
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<td>10 (39)</td>
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<tr>
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<td>16 (60)</td>
<td>15 (61)</td>
<td>.9789</td>
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<td>Dialysis type:</td>
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<tr>
<td>Chronic</td>
<td>3 (75)</td>
<td>23 (86)</td>
<td>16 (63)</td>
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<tr>
<td>Temporary</td>
<td>1 (25)</td>
<td>4 (14)</td>
<td>9 (37)</td>
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<tr>
<td>Calcium, mg/dL: (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ca within normal range (≥ 8.9 mg/dL)</td>
<td>0 (0)</td>
<td>6 (22)</td>
<td>7 (28)</td>
<td>.6081</td>
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<tr>
<td>Ca below normal range (&lt;8.9 mg/dL)</td>
<td>4 (100)</td>
<td>21 (78)</td>
<td>18 (72)</td>
<td>.7110</td>
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<td>Albumin, g/dL: (mean ± SD)</td>
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</tr>
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<td>Albumin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>.6902</td>
</tr>
<tr>
<td>within normal range (≥3.5 mg/dL)</td>
<td>4 (100)</td>
<td>27 (100)</td>
<td>25 (100)</td>
<td>-</td>
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<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Albumin below normal range (&lt;3.5 mg/dL)</td>
<td>4 (100)</td>
<td>27 (100)</td>
<td>25 (100)</td>
<td>-</td>
</tr>
<tr>
<td>PTH, pg/mL: (mean ± SD)</td>
<td>71.5 ± 48</td>
<td>124 ± 86.2</td>
<td>139.9 ± 154.7</td>
<td>.5635</td>
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<tr>
<td>PTH within normal range (&lt;53.5 pg/mL)</td>
<td>2 (50)</td>
<td>6 (22)</td>
<td>7 (28)</td>
<td>-</td>
</tr>
<tr>
<td>Within NKF*** target range (53.5-300 pg/mL)</td>
<td>2 (50)</td>
<td>19 (70)</td>
<td>14 (56)</td>
<td>-</td>
</tr>
<tr>
<td>Above NKF target range (&gt;300 pg/mL)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>.9999</td>
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<td>Patients Diagnosed with D deficiency upon admission</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Patients on vitamin D supplement upon admission</td>
<td>3 (75)a</td>
<td>11 (42)b</td>
<td>4 (16)c</td>
<td>.0268*</td>
</tr>
<tr>
<td>Patients on multivitamin supplement upon admission</td>
<td>1 (25)</td>
<td>5 (18)</td>
<td>3 (13)</td>
<td>.6324</td>
</tr>
<tr>
<td>25(OH)D, ng/mL: (mean ± SD)</td>
<td>42.5 ± 7.4a</td>
<td>16.2 ± 5b</td>
<td>7.1 ± 1.6c</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>1,25(OH)2D, ng/mL: (mean ± SD)</td>
<td>25.1 ± 10.3a</td>
<td>15.6 ± 11.3ab</td>
<td>10.5 ± 3.4b</td>
<td>.0061*</td>
</tr>
</tbody>
</table>

* Indicative of significant difference between groups between groups (p<.05)
** Values expressed as n (%) unless otherwise noted
*** NKF = National Kidney Foundation
abc: means with the same superscripts are not significantly different from each other, means with different superscripts are significantly different from each other
Major medical diagnoses

The frequency of patients’ major diagnoses beyond renal failure at their time of admission can be seen in Table 2. While there were no significant differences between any of the vitamin D sufficiency groups, the high frequency of type 2 diabetes, hypertension and hyperlipidemia in patients with ESRD in this study was notable. Seventy-five percent of group 1, 40% of group 2, and 40% of group 3 were diagnosed with T2DM at the time of admission. Hypertension was diagnosed in 50% of patients in group 1, 33% of group 2, and 20% of group 3. While no patients in group 1 were diagnosed with hyperlipidemia, 40% were in group 2 and 16% were in group 3. Other less frequent diagnoses found in the sample included cardiovascular disease, congestive heart failure and respiratory issues.

Table 2. Comparison between other major diagnoses

<table>
<thead>
<tr>
<th>Major diagnoses:</th>
<th>Group 1 Sufficient (n=4)</th>
<th>Group 2 Insufficient (n=27)</th>
<th>Group 3 Deficient (n=25)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Type 2 Diabetes</td>
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<tr>
<td>Hypertension</td>
<td>2 (50)</td>
<td>9 (33)</td>
<td>5 (20)</td>
<td>.7018</td>
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<tr>
<td>Hyperlipidemia</td>
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<td>11 (40)</td>
<td>4 (16)</td>
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<td>5 (19)</td>
<td>1 (4)</td>
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<tr>
<td>Congestive Heart Failure</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
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<td>1 (3)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td>Condition</td>
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<td>1 (3)</td>
<td>0 (0)</td>
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<td>-------</td>
<td>-------</td>
<td>-------</td>
<td></td>
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<tr>
<td>Lung disease</td>
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<td>1 (4)</td>
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<tr>
<td>Endocarditis</td>
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<td>1 (4)</td>
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<td>GERD</td>
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<td>Crohns</td>
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<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
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<tr>
<td>Colitis</td>
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<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
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<tr>
<td>HIV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
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<td>1 (3)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Spina bifida</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are expressed as n (%)*

*p<.05*

**DISCUSSION**

While there is currently data available on the prevalence of vitamin D deficiency in patients on hemodialysis, the findings from this study add to the literature in that they showed that current guidelines for assessing vitamin D status in CKD patients (e.g., done only with PTH levels >300 pg/ml) may result in many missed cases of vitamin D inadequacy among hemodialysis patients. The data collected from this study showed that patients with chronic and temporary kidney damage are at high risk of having vitamin D insufficiency and deficiency, which puts them at risk for bone fractures as well as type 2 diabetes and hypertension. Study findings also suggest that vitamin D insufficiency and deficiency was unrelated to gender and race, but may be more significant in younger individuals with renal disease. Serum calcium, albumin and PTH levels were not related to 25(OH) vitamin D.

The findings from this study showed that the prevalence of vitamin D insufficiency and deficiency is high in patients on hemodialysis, with 7% of patients having a sufficient vitamin D status, as assessed by serum 25(OH) vitamin D levels >30 ng/mL, 48% having an insufficient level and 45% having a deficient level; therefore, the entire sample in this study had a vitamin D
insufficiency rate of 93%. These findings are comparable to those of other studies conducted both in the United States and abroad on hemodialysis patients in clinical settings. Jean et al. conducted a study in France examining vitamin D deficiency in elderly hemodialysis patients in an acute care setting. These researchers also looked at the association between baseline patient characteristics and vitamin D status. The results of this study showed an 89% prevalence rate of vitamin D insufficiency among participants. Much like the findings in the present study, Jean et al. concluded that there were no demographic, biochemical or clinical characteristics of patients that could predict a high risk of vitamin D deficiency. The study conducted by Jean et al. differs from the present study however, in that only patients who were not on vitamin D supplementation prior to starting dialysis were included and all participants were over 65 years of age. Findings from the present study are also highly comparable to those of Saab et al., whose cohort study of elderly hemodialysis patients was conducted in St. Louis and identified a vitamin D deficiency prevalence rate of 92% prior to supplementation with ergocalciferol.

One very notable finding in this study is that despite the high prevalence rate of vitamin D inadequacy among patients on dialysis, no patient was diagnosed with a vitamin D deficiency by their physician prior to being admitted to a LTACH. This may be due to the fact that the National Kidney Foundation’s guidelines suggest that stage 5 CKD patients only have their 25(OH) vitamin D assessed when PTH levels are above 300 pg/mL. This guideline does not address vitamin D deficiency as much as it addresses the common risk that CKD patients have of developing secondary hyperparathyroidism, which occurs because of the failing kidney’s inability to convert vitamin D to its active form, resulting in hypocalcemia. Because of the inverse relationship between 25(OH) vitamin D and PTH, vitamin D supplementation is thought to be an efficient and safe way to decrease levels that are too high. Findings from this study
showed that almost every patient’s PTH was within the target range, leaving physicians no reason to assess vitamin D status according to guidelines. However it should be noted that 4 patients who had PTH levels above target range were not diagnosed with vitamin D deficiency. With our current knowledge of risks associated with, as well as benefits of vitamin D, it seems that re-assessing these guidelines may be warranted for patients with ESRD.

Another interesting finding in this study was the fact that the vitamin D insufficient group was significantly older than the vitamin D deficient group. While vitamin D deficiency is commonly considered to be more prevalent in older adults, our deficient group had an average age that was ten years younger than the insufficient group. This result, however, may have been skewed by the fact that a significantly larger proportion of the insufficient group was on vitamin D supplementation on admission. Forty-two percent of the insufficient group was on a type of vitamin D supplementation when admitted to The Drake Center, while only 16% of the deficient group was on vitamin D supplementation. The fact that 75% of the sufficient group was on supplementation may be proof that vitamin D supplements in patients with failing kidneys may effectively raise 25(OH) vitamin D levels, however it is hard to draw that conclusion with such a small sample number, as well as without more information on the dosage and types of supplementation.

When looking at other major diagnoses at the time of hemodialysis, no findings were significant. Of importance however, is the fact that 43% of all patients had type 2 diabetes, with hypertension as the next most prevalent comorbidity (29%). While type 2 diabetes and hypertension are both commonly identified as major comorbidities of CKD, they may be further complicated by vitamin D insufficiency. Whether or not this is the case cannot be determined by the present study, but is an interesting question for future research.
Limitations and Future Research

This study was not without limitations. A major limitation of the present study was that it is difficult to determine risk factors for a specific condition (in this case vitamin D insufficiency) using a retrospective study design. This study also had a small sample size and a limited number of patients in the vitamin D sufficient group, reducing the power of the study to detect group differences if they existed. Another drawback is the fact that patients’ other major diagnoses at the time of admission were obtained from medical records, possibly causing misclassification if diagnoses were not properly noted by the admitting physician, or if a patient had a condition that was undiagnosed at the time of admission. The greatest limitation of this study however, is the fact that some of the sample had been receiving vitamin D supplementation upon admission while others did not. While each patient was taken off of supplementation when admitted to the Drake Center, prior supplementation would still affect 25(OH) vitamin D status and may have altered study findings. In the future, a larger sample size based on a power calculation as well as the exclusion of any patient on vitamin D supplementation would be important study design elements to consider in an effort to reach more definitive conclusions. Also, the inclusion of study outcomes such as bone density would be important to determine how vitamin D status impacts bone health in CKD patients being treated with hemodialysis.

Conclusion

Regardless of limitations, it can be concluded that the prevalence of vitamin D deficiency in CKD patients is high. While there are no defining characteristics that indicate who within this population is at a higher risk of having vitamin D insufficiency/deficiency upon admission, it
may be beneficial for nephrologists to assess all CKD patients’ for their vitamin D status regardless of PTH level.

REFERENCES


APPENDIX

DATA DICTIONARY

**25OHD initial:** This value refers to the patient’s first recorded 25(OH)D level in ng/mL.

**1,25(OH)₂D initial:** This value refers to the patient’s first recorded 1,25(OH)₂D level in ng/mL.

**Calcium initial:** This refers to the patient’s first and last calcium reading in mg/dL. The reference range for calcium is 8.9-20.5 mg/dL.

**PTH initial:** This refers to the patient’s first and last parathyroid hormone reading in pg/mL. The reference range for PTH is 7.5-53.5 pg/mL.

**Albumin initial:** This refers to a patient’s first and last albumin reading in g/dL. The reference range for albumin is 3.6-5.1 g/dL.

**Deficiency listed as dx on admission:** Whether a deficiency was noted when the patient was admitted to the Drake Center.

**On D or analogue on admission:** Whether a patient was receiving vitamin D supplementation upon admittance.

**On multivitamin on admission:** Whether a patient was taking a multivitamin at the time of admission.

**Other major diagnoses:** All other major diseases mentioned when patient was admitted to the Drake Center.

**T2DM:** Listed if the patient had type 2 diabetes mellitus upon admittance to the Drake Center.

**HTN:** Listed if the patient had hypertension upon admittance to the Drake Center.

**HL/DL:** Listed if the patient had dyslipidemia upon admittance to the Drake Center.