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The Observational Investigation of Vitamin D and the Effect on Hypertension (OIVEH) Study

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Scholarly Project

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DEDICATION

This project would not have been possible without my wife, Marisol, who has never doubted my abilities, and to my mom, who set me on the educational pathway at a young age.

ABSTRACT

Background

It is uncertain if vitamin D supplementation improves cardiovascular health, more specifically, the systolic and diastolic blood pressures, and the data from previous trials investigating supplementation and the effects on the blood pressure are limited.

Methods

The following scholarly project was a retrospective observational study, examining randomly selected participants with chronic kidney disease and hypertension from a local nephrology practice. The Student's *t*-test, Pearson's *r* correlation, and ANOVA statistical tests were utilized to determine if vitamin D supplementation improved the systolic and diastolic blood pressures.

Results

A total of 260 participants were examined. The mean systolic blood pressure of patients using vitamin D supplementation (M = 139.72, SD = 21.69, N = 125) was not significantly different from those without vitamin D supplementation (M 136.67, SD 21.62, N= 135) t(258) = -1.136, p = 0.752). The mean diastolic blood pressure of patients using vitamin D supplementation (*M* = 82.90, SD 12.28, *N* = 125) was not significantly different from those without vitamin D supplementation (*M* = 82.91, SD 11.22, *N* = 135) t(258) = -2.84, p = 0.565).

Conclusion

In this retrospective observational study, supplementation with vitamin D did not result in a statistically significant reduction in the systolic or diastolic blood pressures when compared to those who did not take a vitamin D supplement. Future research, which may

benefit from considering the confounding variables identified in this study, may provide the needed data to determine if vitamin D supplementation could improve the systolic and diastolic blood pressures in those with CKD.

KEY WORDS: *cholecalciferol, ergocalciferol, vitamin D3, vitamin D2, 25-hydroxyvitamin D3, 1,25-dihydroxyvitamin D3*

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Chapter One

Introduction

The nature of the kidney's biological role is complex. As a result, any disease state that affects kidney function will affect other organ systems. This includes acute and chronic kidney disease. The plethora of downstream issues, brought about by kidney disease, is a public health concern. The number of Americans with chronic kidney disease (CKD) is estimated to be 30 million in 2017 and is projected to increase (CDC, 2017). CKD is a nationally significant public health dilemma.

The prevalence of CKD in the United States for individuals over the age of 30 has reached over 13%, and is expected to increase to over 14% by 2020, and rise to 17% by 2030 (Hoerger et al., 2015). The chronicity of the disease leads to other health issues and includes, but is not limited to anemia, metabolic derangements, worsening of cardiovascular disease, and vitamin D deficiency. CKD, and the inevitability of these complications, causes a tremendous burden on the American healthcare system and its' resources. In 2015 alone the total cost for CKD, which included end stage renal disease (ESRD), was over $98 billion Medicare dollars (United States Renal Data System, 2017).

One complication, Vitamin D deficiency, is almost ubiquitous in the ESRD population, and affects upwards of 80% of the pre-dialysis CKD population (Caravaca-Fontan, Gonzales-Candia, Luna, & Caravaca, 2016). CKD affects over 30 million Americans, or 15% of the population. One out of every seven American adults is thought to have chronic kidney disease, and one in three are at risk (CDC, 2017). The increasing frequency of CKD in the population has caused it to be one of the predictors for the incidence of cardiovascular disease and associated mortality. Further, when comparing

individuals with CKD to the general population, those with CKD have a significantly higher frequency of vitamin D deficiency (Lishmanov et al., 2013). The higher incidence of this deficiency is linked to reduced intake of vitamin D fortified foods, lessened cutaneous synthesis via skin exposure to UV-B radiation, and a reduced number of functional nephrons. As a result, the deficiency of the precursors (ergocalciferol and cholecalciferol) plus the reduced number of nephrons seen in those with CKD causes the sharp decline in the conversion of 25-hydroxyvitamin D3 (cholecalciferol) to 1,25-dihydroxyvitamin D3 (calcitriol). As a result, it is hypothesized that a deficiency in serum 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 is linked to hypertension via the up-regulation of the renin-angiotension-aldosterone-system (RAAS), and endothelial dysfunction, which is identified in the literature as vascular stiffness.

Vitamin D, and its ability to produce more than one benefit, is an area for further study. The mechanisms for vitamin D deficiency have not been fully elucidated, but evidence implies a strong inverse association between the serum concentration of vitamin D and morbidity and mortality in the CKD population (Navaneethan et al., 2011). The odds of a cardiovascular event among the patients treated with Vitamin D were 0.32 times lower than the odds among the untreated group (95% CI: 0.13-0.79, $p = 0.01$) (Lishmanov, Dorairajan, Chaudry, and Chockalingham, 2013).

Vitamin D is essential in bone metabolism, acts on the cardiovascular and immune systems, is associated with diabetes, and even suppresses malignant cells (Mazzaferro & Pasquali, 2016). The multiple roles of vitamin D, and its subsequent deficiency, bring about the high incidence of morbidity and mortality in the CKD population. This scholarly project aims to review vitamin D metabolism, review available

literature related to Vitamin D and hypertension, conduct a retrospective observational study of patients with CKD stages one through five, and make recommendations to improve vitamin D supplementation in an effort to improve hypertension in the CKD population.

Vitamin D Metabolism

Vitamin D and its metabolites are not true vitamins, but fat-soluble hormones with specific receptor sites located virtually in every cell within the human body (Jean, Souberbielle, & Chazot, 2017). Humans acquire approximately 80% of the needed hormone through cutaneous synthesis brought about by sunlight, or more specifically, ultraviolet light-B (UVB) exposure, while the rest may come from dietary sources and supplementation. UVB exposure causes 7-dehydrocholesterol to be spontaneously transformed to cholecalciferol (D3) in the skin. A circulating vitamin D binding protein provides a mechanism to remove vitamin D from the skin and make it available to the liver. In the liver, the cholecalciferol is hydroxylated to form 25-hydroxyvitamin D3 (25-(OH)D3. Circulating 25-(OH)D3 is transported to the renal tubules where it undergoes conversion to 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] (Mazzaferro & Pasquali, 2016). Oral supplementation can be via plant-based vitamin D, which is ergocalciferol (D2), as well as animal sourced vitamin D, which is cholecalciferol (D3). The two oral sources differ by the presence of a double bond, but have identical biologic activity (Jean, Souberbielle, & Chazot, 2017). The dietary and supplement sources of vitamin D, like the cutaneous derived vitamin D, are also transported to the liver for conversion to 25-hydroxyvitamin D3, and then transported to the renal tubules for conversion to 1,25-dihydroxyvitamin D3.

Interestingly, the kidneys are not the sole producers of 1,25-dihydroxyvitamin D3. Other sites where 25-hydroxyvitamin D3 is converted to 1,25-dihydroxyvitamin D3 includes parathyroid cells, macrophages, osteoblasts, smooth muscle cells, endothelial cells, and tissues such as the pancreas, breast, prostate, and colon (Cardoso & Pereira, 2018). Although there are areas outside of the kidney that produce 1,25-dihydroxyvitamin D3, the kidney is the dominant source for the hormone (Cardoso & Pereira, 2018). The renal and extra-renal production of 1,25-dihydroxyvitamin D3 is the most potent of the vitamin D metabolites, which plays a role in regulating the function of other systems involved in calcium homeostasis. The most common understanding of this metabolite is that it increases intestinal absorption of calcium and promotes the actions of parathyroid hormone (PTH) on resorption of calcium and phosphate from the bone. One other, lesser known, physiologic effect of this hormone is the inhibitory effects on the renin-angiotensin system, resulting in mediating hypertension as it has been uncovered that there is an inverse correlation between plasma vitamin D and plasma renin activity and angiotensin II levels (Mazzaferro & Pasquali, 2016 and Zhang et al., 2018).

PICO Question

The question remains, in the individual with CKD, does vitamin D supplementation, compared to no supplementation, improve the systolic and diastolic blood pressures? To answer this research question, the researcher proposes a retrospective observational study to determine the effects of vitamin D on individuals with CKD and hypertension.

Theoretical Framework

In an effort to direct this scholarly project, Vitamin D supplementation and its'

effects on hypertension will be investigated utilizing Betty Neuman's Systems Model nursing theoretical framework. In this observational study, the client with chronic kidney disease (CKD) will occupy the core. The lines of defense will be represented by primary, secondary, and tertiary prevention strategies, as well as the identification of stressors coming into contact with the lines of defense. According to Neuman's model, the client suffers illness or disease when the lines of defense and resistance are compromised, and the individual can no longer maintain homeostasis (Butts & Rich, 2015). In this scholarly project, the threat to homeostasis will be the lack of sufficient vitamin D stores. When there are compromises in the lines of defense and resistance, and a threat to homeostasis is considered, nurse practitioner interventions are required in order to allow the reconstitution of the lines and bring about homeostasis.

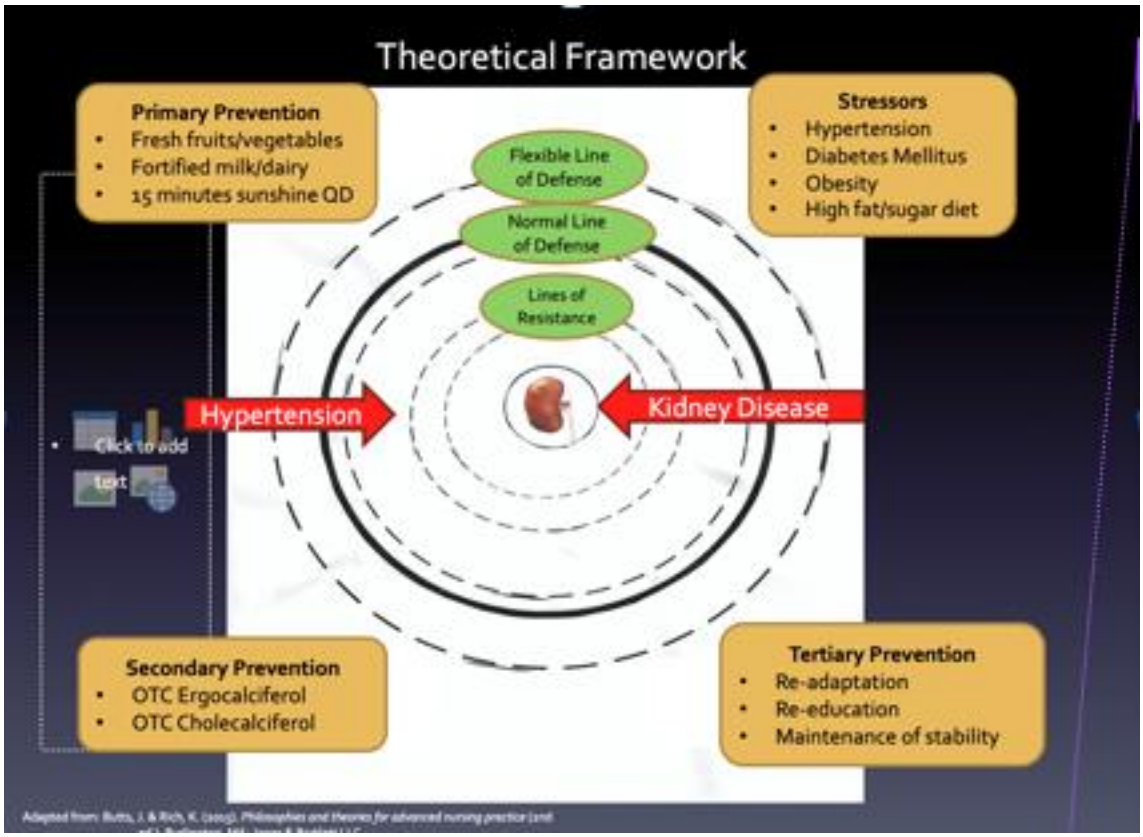

Figure 1.1 - Theoretical Framework

Chapter One Summary

Vitamin D is the only substance, identified as a vitamin, which can be directly synthesized by the human body. Areas within the human body, which synthesize 25-hydroxyvitamin D3 (cholecalciferol) to its active form, 1,25-dihydroxyvitamin D3 (calcitriol), include the kidneys, parathyroid cells, macrophages, osteoblasts, smooth muscle cells, endothelial cells, and tissues such as the pancreas, breast, prostate, and colon. The mechanisms that may improve the availability of the precursor, 25-hydroxyvitamin D3, include oral ingestion, as well as increased UV light exposure to the skin of the human. Increasing evidence suggests that vitamin D plays a larger role in whole body homeostasis. One such area is the renin-angiotensin-aldosterone system, and the role that vitamin D plays in moderating hypertension. As a result of any, or all, of the above interventions, would the improved serum concentrations of 25-hydroxyvitamin D3, and ultimately 1,25-dihydroxyvitamin D3 be sufficient to assist in the palliation of hypertension in the CKD population?

Chapter Two

Introduction

Vitamin D is a fat-soluble secosteroid hormone that has a specific receptor (VDR) on almost every human cell. This mechanism of action is involved in almost three percent of the human genome through gene expression or suppression (Jean, Souberbielle, & Chazot, 2017). Vitamin D is not only a predictor of bone health, but is also coupled with hypertension, endothelial dysfunction, metabolic derangements, immunologic health, and oncological disorders (Lishmanov, Dorairajan, Pak, Chaudhary, & Chockalingham, 2013). A low serum 25-hydroxyvitamin D3 has been linked to higher cardiovascular events, cardiovascular disease mortality, and all-cause mortality (Melamed, Michos, & Post, 2008). The implication of these findings should be directly observable in a population that can have chronically suppressed vitamin D levels from a reduction in functional nephron units.

Review of the Literature

To determine if there is a significant relationship between vitamin D and hypertension, academic and research literature will be investigated. Relevant literature was reviewed for the past five years ranging from 2013 to 2018 from the following databases: PLoS One, ClinicalKey, CINAHL complete, and PubMed. Selected articles and studies in the review of literature had to meet certain criteria to be included. These criteria included a publish date within the previous five years, peer reviewed, full text availability, and be available in the English language. This review of the literature took place between the months of September to November of 2018. The inquiry included the following key words and headings: vitamin D, 25-hydroxyvitamin D3, 1,25-

dihydroxyvitamin D3, vitamin D and hypertension, vitamin D and endothelial, vitamin D and renin-angiotensin, vitamin D and sunlight exposure, and vitamin D and cardiovascular. MeSH terms for vitamin D and kidney disease were explored. Searched information was limited to literature reviews, comprehensive reviews, systematic reviews, and clinical trials. An extended search was carried out, in order to ascertain the pathophysiological processes of vitamin D, utilizing the National Institute of Health, the Centers for Disease Control, the Food and Drug Administration, and Up-To-Date, as well as medical textbooks and non-fiction science books.

Significance of Association of Vitamin D to Hypertension

Vitamin D is an important facilitator of calcium metabolism and is acquired via dietary sources and UV-B radiation. The key indicator of sufficient stores of vitamin D within the body is 25-hydroxyvitamin D, which is converted to its active form 1,25 dihydroxyvitamin D3 within the kidney. 25-hydroxyvitamin D3 and 1,25 dihydroxyvitamin D3 are vitamin D receptor (VDR) agonists, but it is the active form, 1,25-dihydroxyvitamin D3 that is the most potent analogue. Vitamin D receptors (VDR) are found on almost every type of tissue within the body (Vaidya & Williams, 2012). Once 1,25 dihydroxyvitamin D3 is bound to the VDR, a chain of events occurs in which the phosphorylated complex then affects gene transcription and expression on and within cellular structures. In regards to amelioration of hypertension, the phosphorylated complex within the juxtaglomerular cells of the nephron suppresses renin expression, thereby interfering with the RAAS cascade (Mehta & Agarwai, 2017).

Vitamin D supplementation on endothelial function was the focus of a meta-analysis by Hussin, Ashor, Schoenmakers, Hill, Mathers, and Siervo (2016). The

researchers searched Medline, Embase, Cochrane Library, and Scopus databases and chose 16 studies that reported data on 1177 participants. The duration of the studies ranged from four to fifty-two weeks. The studies consisted of 607 females and 570 males with a median age of 73. All trials supplemented vitamin D orally via solution, capsules, biscuits, or tablets. Flow Mediated Vasodilation (FMD) measured the response to endothelial function. FMD is a measurement of how the blood vessels respond to an increase in flow, or the shear stress, by dilating. Vitamin D supplementation improved endothelial function significantly in those with type 2 diabetes, $p = 0.02$. This was determined to be a result of endothelial cell dependent vasodilatation, which is mediated by the effect of the vitamin D3 and VDR on the renin-angiotensin-aldosterone system. A low serum 25-hydroxyvitamin D3 predisposes to up-regulation of the renin-angiotensin system, smooth muscle proliferation, and favors a pro-inflammatory state, which contributes to hypertension.

The effect of vitamin D supplementation on brachial artery compliance was studied by Zhang et al. (2017). A total of seventy-one CKD patients with a serum 25-hydroxyvitamin D3 [25(OH)D3] level less than 30ng/mL were enrolled. There was significant increase in serum levels of 25(OH)D3 after cholecalciferol supplementation with 50,000 units once a week for 12 weeks, $p < 0.0001$. Higher incidences of proteinuria, measured by 24 hour urine collection for protein, were associated with lower levels of serum 25(OH)D3, $p < 0.001$. A vitamin D deficiency was associated with a decreased brachial artery flow-mediated dilation (FMD). A decrease in FMD results, as there are fewer vitamin D3 and VDR complexes regulating gene expression causing less accommodation to the sheer stresses within the arteries and leading to higher incidences

of hypertension, $p < 0.001$

The role of vitamin D on the inhibition of renin production was studied, by Deng, Cheng, and Shen (2016), using 50 male Sprague-Dawley rats. Five rats were the control group (NC), while 45 rats became the diabetic group (DN). The 45 rats designated to be the diabetic nephropathic group were induced via intraperitoneal streptozocin injection. The 45 rats were further subdivided into four experimental groups, which were diabetic nephropathy with no treatment (DN), diabetic nephropathy with irbasartan (DNI), diabetic nephropathy with calcitriol (DNC), and diabetic nephropathy with irbasartan and calcitriol (DNIC). Vitamin D combined with irbasartan exerted a synergistic effect on the treatment of diabetic nephropathy, where the combined treatment more effectively ameliorated diabetic nephropathy than irbasartan alone. Further, vitamin D is thought to combine with the vitamin D receptor (VDR), creating a complex, thereby down regulating or suppressing renin gene expression, reducing systemic inflammation, and reducing the blood pressure (Kota et al., 2011).

To better understand the impact of calcitriol on the circulating renin-angiotensin systems and reno-vascular hemodynamics, Zaheer et al., (2017) performed a double-blinded randomized controlled trial on 18 participants with well-controlled type-2 diabetes mellitus. The study participants' anti-hypertensive medications were discontinued over a washout period of two months. After the washout period, the participants were prescribed a diet with fixed amounts of sodium, potassium, and calcium for one week. During a second week, the sodium content of the diets was classified as restricted or liberalized, and randomly administered to subjects. After the week of randomized sodium diets the subjects were admitted to the research center where subjects

remained in a supine position overnight, then assessed at 0800 A.M. the next day. This interesting methodology was instituted to assess the baseline suppressed renin-angiotensin system, blood pressure, and mean arterial pressure. The participants were then randomized into either the calcitriol or placebo groups. Following the randomization, participants were to receive either calcitriol 0.25 micrograms or a placebo as a pill. Subjects returned at weeks four, five, and six for blood pressure and MAP assessment. Also, serum calcium, phosphate, creatinine, PTH, 25-hydroxyvitamin D, and urine electrolytes were measured. The authors hypothesized that supplementing with the active form of vitamin D (calcitriol) and the resulting vitamin D receptor agonist activity would down regulate the renin-angiotensin system thereby improving hypertension. The controlled trial lasted approximately thirteen weeks, with the last three weeks encompassing the intervention phase of the study.

Zaheer et al. (2017) found that in well-controlled diabetics with a normal serum 1,25-dihydroxyvitamin D3 (calcitriol) that there was not a significant improvement of the systolic pressure, diastolic pressure, or the mean arterial pressure, $p = 0.91, 0.91, 0.90$ respectively. Also, a low salt diet, when compared to a restricted salt diet combined with calcitriol administration did not improve plasma renin activity, nor serum aldosterone levels, $p = 0.54, 0.57, 0.59$, and 0.36 respectively.

The Zaheer et al. (2017) study did not uncover evidence that calcitriol administration improved hypertension, but the study is not without criticism. Firstly, this study bypasses the kidney's role as the main converter of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3. Secondly, the study subjects had a normal serum vitamin D3 level at the initiation of the study.

The paricalcitol and endothelial function in chronic kidney disease (PENNY) in stages three and four was examined by Torino et al., (2017). The study proposed that vitamin D could ameliorate the levels of pentosidine, a low molecular weight advanced glycation end products (AGE) implicated in cardiovascular disease and advancing renal damage in individuals with CKD. Initially, the PENNY trial was developed to ascertain the effects of vitamin D on the oxidative stress pathways within the individual with CKD. These oxidative pathways are advanced glycation end products (AGE) and the receptors of AGE (RAGE).

The study by Torino et al. (2017) was unable to show that 1,25-dihydroxyvitamin D3 was able to modify the biomarkers of the AGE and RAGE system or other biomarkers of oxidative stress, such as myeloperoxidase in the CKD patient. The study did not show a reduction in the described biomarkers, but it did demonstrate an interesting trend. The C-reactive protein was more than double in the placebo group versus the active group, 2.49 versus 1.18 respectively, $p = 0.11$. Although it was not considered statistically significant the reduction was evident none-the-less. Interestingly, the p-value approached significance, indicating the study may have been underpowered.

Flow mediated vasodilatation (FMD) and its effects on individuals with stages three and four of chronic kidney disease was analyzed by Lundwall, Jacobson, Jorneskog, and Spaak (2018). Flow-mediated vasodilatation is an ultrasonographic image, via handheld ultrasound imaging, of the brachial artery, whereby the procedure triggers the release of nitric oxide. The release of nitric oxide and the resulting vasodilatation can be quantitated as an index of vasomotor function (Corretti et al., 2002). The non-invasive technique allows for repeatability over time to study the effectiveness of various

interventions. FMD is a measure of utility and not organization, thus it can be interpreted as an early sign of vascular disease, and likely more amendable by shorter durations of treatment, i.e. vitamin D replacement (Lundwall et al., 2018). Three of the five studies included in this meta-analysis favored the treatment with vitamin D replacement. Intervention with vitamin D improved flow-mediated vasodilatation (95% CI; 0.55-1.01) (Lundwall et al., 2018).

In a meta-analysis of 20 trials by Kaur, Singh, and Kumar in 2018, vitamin D and the role it may play in cardiovascular health in the CKD population was examined. The various studies surveyed systolic and diastolic blood pressure, ambulatory blood pressure, left ventricular hypertrophy, flow-mediated vasodilatation, left ventricular mass index, IL-6, CRP, MCP-1, FGF23, and homocysteine. Of the 20 studies examined, 18 of those studies show an improvement in cardiovascular health. These studies also revealed an improvement of the systolic and/or the diastolic pressure, in some form, as evidenced by a reduction in left atrial volume, left ventricular mass index, mean pressures, or an increase in FMD when the vitamin D intervention is instituted.

The effect of vitamin D supplementation for CKD patients was studied to ascertain vascular stiffness, blood pressure, mineral metabolism, C-reactive protein (CRP), and fibroblast growth factor 23 (FGF-23) (Levin et al., 2017). Vitamin D supplementations of 1,25-dihydroxyvitamin D3 (calcitriol) and 25-hydroxyvitamin D3 (cholecalciferol/calcifediol) were compared to placebo on vascular stiffness, as measured by non-invasive pulse wave velocity (PWV).

Levin et al. (2017) found the PWV diminished in the calcifediol group (mean change, -1.1; 95% CI, -2.2 to 0.1 m/s), remained unaffected in the calcitriol group (mean

change, 0.2; 95% CI, -0.9 to 1.4 m/s), and escalated in the placebo group (mean change, 1.1; 95% CI, -0.1 to 2.2 m/s). The between-arm changes were significant among the groups, $p = 0.03$. In other words, the use of the vitamin D analog, cholecalciferol or calcifediol, improved pulse-wave velocity, trended towards improvement of measured vascular stiffness, and improved blood pressures. Of note, the researchers did not attempt to utilize vitamin D as a sole anti-hypertensive agent.

Chapter Two Summary

Observational studies have shown an association between vitamin D deficiency in CKD and cardiovascular diseases. Despite this association, the disparities in the study designs of randomized clinical trials, small sample sizes, logistical variations, homogeny among study participants, extent of the intervention, and the lack of consistency among the vitamin D preparations utilized in the above mentioned studies, it will be challenging to offer definitive recommendations about vitamin D replacement strategies. Although some of the results may not have offered statistical significance the reduction in blood pressure and some biomarkers, such as C-reactive protein, were evident, which signifies many of the studies were underpowered.

Chapter Three

Experimental Design

The proposed non-experimental retrospective observational study will be used to find if vitamin D supplementation, compared to no supplementation, improves the systolic and diastolic blood pressure. The study is quantitative in nature because the study will be examining the relationship between variables. Retrospective in that data, from chart reviews, will be examined from previous points in time, also because, potentially, a phenomenon existing in the present, i.e. hypertension (ICD-10 code I12.9), is linked to phenomena that occurred in the past, i.e. low serum cholcalciferol (ICD-10 code E55). The researcher will begin with the dependent variable, i.e. hypertension , and then examine whether this is correlated with one or more previously occurring independent variables, i.e. serum cholcalciferol. This scholarly project will be non-experimental. The researcher will be a passive observer, and will not be manipulating the variables, or administering a treatment.

The intended non-experimental design will be examined for the three criteria for causality. These include temporal, which is that a cause must come before the effect in time; an empirical relationship, which is the question of is there an association between the variables; and finally, that the relationship cannot be explained by a third variable. Due to the nature of the project, time constraints, and the absence of ancillary research staff, the criteria for causality may not be established in short order. In order to offset this inevitable outcome there is the principle of biologic plausibility, in that there are physiologic phenomena that a causal route is credible. Ultimately, the study will seek to ascertain if a relationship between hypertension and serum vitamin D3 levels exists.

Population Examined

The groups examined were those with CKD stages one through five. The inclusion criteria will be that they are English speaking, will have CKD one to five, have a diagnosis of hypertension, are on at least one anti-hypertensive agent, are over the age of 21, and have a systolic and diastolic blood pressure reading with a concurrent serum cholecalciferol level at the time of follow up. The stages of CKD will be assessed according to the estimated glomerular filtration rate (eGFR), and are as follows: a) stage I with an eGFR 90mL/min. or higher; stage II with an eGFR 89 - 60mL/min.; c) stage III with eGFR of 59 to 30mL/min; d) stage IV CKD with an eGFR of 29 to 15mL/min.; and e) stage V with an eGFR 15mL/min. or less. The 25-hydroxyvitmin D3 (cholecalciferol) levels will be based on the reference levels as defined by the Institute of Medicine (IOM) as: a) deficiency: less than 20 ng/mL; b) borderline: 20-29 ng/mL; c) optimum: 30-80 ng/mL; and d) possible toxicity: >150ng/mL (Holick et al., 2011). The exclusion criteria will include those who are not English speaking, those who do not have a diagnosis of hypertension, those who take an angiotension converting enzyme inhibitor (ACEI) or an angiotension receptor blocker (ARB) for proteinuria without a diagnosis of hypertension, those with a diagnosis of medical non-compliance with an ICD-10 code of Z91.1, those under the age of 21, the terminally ill, the mentally incompetent, pregnant individuals, those with a diagnosis of sarcoidosis, and active malignancy, or an active thyroid disease.

Origination of Data

Permission and clearance to observe patient data for this proposed scholarly project has been obtained from Nephrology Associates. Nephrology Associates is a private nephrology practice comprising of fifteen physicians, and ten nurse practitioners

serving the Southeast Tennessee and North Georgia areas. The prospective subjects will be obtained from the Nephrology Associates' electronic medical record (EMR) database of over 10,000 active CKD patients. Assistance will be obtained from the Southeast Renal Research Institute, a division of Nephrology Associates based in Chattanooga, Tennessee. A software program, identified as Saama, will be utilized to select prospective patients based on inclusion and exclusion criteria. Saama will query the EMR, NextGen, in order to obtain the necessary information. The data mining within medical records can present a risk for private heath information to be exposed causing potential HIPPA violations. To this end, steps have been taken to negate the possible breech of privacy.

Protecting Human Subjects and Sensitive Health Information

The proposal for this project scholarly project has been evaluated, and permission has been granted by the Institutional Review Board (IRB) to proceed. The participants chosen for observation did not include a name, a date of birth, a social security number, nor a medical record number. The individuals were listed by sequential numerical values beginning with one. The variables recorded include, but are not limited to gender, age, race, systolic and diastolic blood pressure measurements, serum cholecalciferol level, and the stage of CKD based on eGFR. The study did not include vulnerable populations of people as listed in the exclusion criteria. All patient identifiers were removed and replaced with a single identifying number. A random number generator was utilized to select individuals to examine. The acquired data was archived and catalogued onto a single USB memory drive dedicated for this scholarly project.

Statistical Measurements

There are four groups that will be included in the proposed study. These include: a) high blood pressure and a low serum vitamin D (HTNlowD); b) high blood pressure and normal serum vitamin D (HTNnormD); c) normal blood pressure and low serum vitamin D (NBPlowD); and d) normal blood pressure and normal serum vitamin D (NBPnormD). This study will employ the one-way ANOVA in order to decrease the chances of a Type 1 error. In this way, the question to be answered will be are the means of the groups significantly different from each other? If the data does not meet the assumptions for the one-way ANOVA, then the Kruskal-Wallis H will be utilized.

The null hypothesis (H_O) is that there will be no difference in serum cholecalciferol levels and hypertension. The alternate hypothesis (H_A) will be that a normal serum cholecalciferol level will correlate to controlled hypertension. This project will utilize the Pearson *r* correlation, which is a bivariate analysis that measures the strength of association between two variables (hypertension and serum cholecalciferol) and the direction of that relationship. The direction determines the association whether negatively, inversely, no relation, or a positive relation. This statistical measurement will help to uncover if there a link between serum cholcalciferol, measured in ng/mL, and blood pressure, measured in mmHg. Assumptions would have to be that both variables should be normally distributed, have linearity (straight line relationship), and homoscedasticity (data is equally distributed about the regression line).

In all, the significance level will be set at the 0.05 level, which if the calculated test statistic happens by coincidence 5% of the time or less, the null hypothesis will be

rejected. Based on previous experimental and non-experimental study data, it is hypothesized that the data will be different among the groups.

Sufficient Power

The determination of an adequate sample size and sufficient power is needed. The previous studies, examined prior to this projected study, have many different sample sizes, and thus varying strength. This proposed study will utilize a moderate effect size of .50, and a power of .80 (Polit & Beck, 2012). To achieve the moderate effect size the total N is based on the Cohen table for two-tailed testing and will be at least 256 individuals (Polit & Beck, 2012).

Data Collection

Retrospective data were collected from Nephrology Associates using an advanced data analytic search engine that enables a business entity to mine stored data within the proprietary computer servers. The previously outlined inclusion and exclusion criteria were input to narrow the search results as a total of 13,353 individuals were identified in the electronic medical record. Of this total, 942 met the criteria for this observational study, were placed within an Excel spreadsheet, and saved to a secure USB drive. A random number generator was utilized and a final number of 260 patients were isolated to be investigated. Medical records were reviewed from August 2019 until December 2019. The data collected was the most recent available at the time of observation, but the data ranged from 2014 to 2019.

Variables Catalogued in SPSS

A total of ten variables were cataloged in to the SPSS program. These variables include: a randomly assigned identification number, age, race, gender, estimated glomerular filtration rate (eGFR), serum 25-hydroxyvitamin D level, whether or not a vitamin D supplement is being taken, the dosage of vitamin D supplement taken, and the systolic and diastolic blood pressures. The serum 25-hydroxyvitamin D level is an independent variable and the reference range is based upon the Institute of Medicine's guidelines for vitamin D supplementation (Holick, 2017). The category of vitamin D supplement is also an independent variable and was refined to include the dosages of vitamin D supplementation. The dependent variables are the systolic and diastolic blood pressures and are recorded in SPSS as a numerical value regardless of characteristic, i.e. hypo, normo, or hyper. The co-variables include age, race, gender, and eGFR.

Strength and Weakness

The observational study has certain weaknesses. Firstly, the study will be working with pre-existing data and individuals, which are not formed at random. Secondly, there may be a variable that would be unaccounted for which may influence the independent and dependent variables. Finally, due to the nature of the proposed study, the sample size may not be sufficient. Alternatively, there are strengths to be considered. The proposed study has the potential to examine numerous variables and potentially larger amounts of data when compared to a randomized controlled trial. Another potential strength could be the study will not be exclusively focused understanding a causal relationship. The proposed study is to bring to light the possible connection between 25-hydroxyvitamin D3 and hypertension.

Chapter Three Summary

The population within the United States is advancing in age and living with chronic diseases, especially CKD, longer than previous generations (CDC, 2017). The main cause for CKD, and eventually ESRD, in this area of the United States is hypertension (CDC, 2017). A vitamin D3 deficiency has been identified as a potential contributor to hypertension. The pathogenesis of a vitamin D3 deficiency can be considered multifactorial, but as CKD progresses the biological means to convert vitamin D3 to its active form decreases. As a result of the decrease in vitamin D3 production the likelihood of persistent hypertension increases, and thus a vicious cycle has been identified. The proposed study will examine a random number of individuals within the Nephrology Associates electronic medical record system who meet the inclusion and exclusion criteria. The utilization of the one-way ANOVA and the Pearson *r* statistical tests will hopefully shed light on the theorized connection between vitamin D3 and hypertension. Whether there is an association or not, the outcome of this study will assist in developing an evidence base to draw causal inferences, and will help with future research.

Chapter Four

Introduction

The identified 260 patient records had the diagnosis of chronic kidney disease and hypertension. The stages of CKD were assessed according to the estimated glomerular filtration rate (eGFR), and are as follows: a) stage I with an eGFR 90mL/min. or higher; b) stage II with an eGFR 89 - 60mL/min.; c) stage III with eGFR of 59 to 30mL/min; d) stage IV CKD with an eGFR of 29 to 15mL/min.; and e) stage V with an eGFR 15mL/min. or less. The study sample had representations from all five stages of CKD, with stage III CKD representing the largest segment with 127 people (See Table 4.1). The ages of the sample ranged from 21 to 78 (M = 51, SD 9.67, N = 260). Caucasians represented 72.7% of the study population, followed by Black at 25.8%, and Hispanic and Asian together were 1.5%. There were 118 females and 142 males with none identifying as transgender. Those identified as not taking a vitamin supplement comprised 51.9% of the study population. The number of people with a serum 25-hydroxyvitamin D level of less than 30 nmol/L totaled 150 people, or 57.6% of the study population, (M = 29.22, SD 13.82, N = 260). Systolic blood pressures ranged from 72mmHg to 215mmHg, (M = 138, SD 21.7, N = 260), and diastolic blood pressures ranged from 46mmHg to 137mmHg (M = 82.9, SD 11.7, N = 260).

Table 4.1 - Demographic and Clinical Characteristics

Age - year	**Range: 21 – 78**
	***M* = 51**
	***N* = 260**
Race – no. (%)	
Caucasian	189 (72.7)
Black	67 (25.8)
Hispanic/Asian	4 (1.5)
Gender – no. (%)	
Male	142 (54.62)
Female	118 (45.38)
Transgender	0
Serum 25(OH)D - nmol/L	*N* = 260
	Range: 5 to 87
<30 nmol/L – no. (%)	150 (57.6)
	M = 29.22
CKD Stage – no. (%)	*N* = 260
I: 90 ml/min or greater	9 (3.5)
II: 60 – 89 ml/min	59 (22.7)
III: 30 – 59 ml/min	127 (48.8)
IV: 15 – 29 ml/min	48 (18.5)
V: 15ml/min or less	17 (6.5)
	M = 46.96
Blood Pressure	*N* = 260
Systolic - mmHg	Range: 72 to 215
	M = 138.13
Diastolic - mmHg	Range: 46 to 137

	M = 82.9
Oral Vitamin D – no.	
No supplement	135
Up to 1K	36
Up to 2K	46
Up to 3K	0
Up to 4K	8
5k and above	35

Analysis of Results

The primary aim this retrospective observational study was to determine if vitamin D supplementation had an effect on blood pressures, but more specifically, does the supplementation in those with CKD, compared to no supplementation, result in improved systolic and diastolic blood pressures? The SBP and DBP histograms reasonably suggest this data is not from a normal population. Although not a perfect fit, the histograms, except for supplement dose of vitamin D, appeared to have a normal distribution. In this study, the data were analyzed with the outliers. The serum vitamin D ranged from 5 to 87 with a median (interquartile range) of 28 (15). The SBP ranged from 72 to 215 with a median (interquartile range) of 138 (28). The DBP ranged from with a median (interquartile range) of 82 (16). The majority of the data follows a normal distribution, the sample size is relatively small, and the population being examined is not a normal population.

Systolic Blood Pressure

The outcome measure was the systolic blood pressure, and if taking a vitamin D supplement had an effect. Did Vitamin D supplementation affect systolic blood

pressures? A two sample student's *t* test using a pooled estimate of the variance was performed to test the hypothesis that systolic blood pressure means would be improved by vitamin D supplementation. The mean systolic blood pressure of patients using vitamin D supplementation (M = 139.72, SD = 21.69, N = 125) was not significantly different from those without vitamin D supplementation (M 136.67, SD 21.62, N= 135) t(258) = -1.136, p = 0.752). A 95% confidence interval on the difference between the two population means using a Student's *t* distribution with 258 degrees of freedom is [-8.35, 2.24], which indicates that there is not significant evidence that a vitamin D supplement impacts SBPs in this study population.

An evaluation of the linear relationship between supplementation and SBP was measured using Pearson's correlation. An analysis of the Pearson's correlation coefficient indicated that there is a small and non-significant linear relationship between vitamin D supplementation and SBP, r(258) = 0.07, $p = 0.26$. For these data, the mean (SD) for SBP was 138.13 (21.66) and for Supplement was 0.48 (0.50).

To delve deeper into the potential effects of vitamin D supplementation and blood pressures, the supplementation variable was recoded with the various dosages of oral vitamin D. The dosages were recoded as: a) Up to 1K, b) Up to 2K, c) Up to 3K, d) Up to 4K, and e) over 5K. To this end, does the dosage of vitamin D affect the systolic blood pressure? A one-way ANOVA was performed to examine systolic blood pressure and the vitamin D dosage. The average systolic blood pressures were found to be similar across methods F(4, 255), p = 0.71. The Tukey multiple comparisons performed at the 0.05 significance level found that the mean systolic blood pressure without supplementation was not significantly different across the treatment groups. The mean systolic blood

pressure for the no supplementation group had a mean of 136.67 with a SD of 21.62. The lowest systolic blood pressure was found in the up to 4K dosage group (M = 133.6, SD = 20.22, N = 8) and the highest systolic blood pressure was found in the up to 2K dosage group (M = 141.2, SD 21.23, N = 46). Mean systolic blood pressures with varying dosages of vitamin D supplementation were not found to be significantly different from each other.

Diastolic Blood Pressure

Did vitamin D supplementation affect the diastolic blood pressures? The outcome measure was the diastolic blood pressure, and if a vitamin D supplement had any effect. A two sample student's t test using a pooled estimate of the variance was performed to test the hypothesis that diastolic blood pressure means would be improved by vitamin D supplementation. The mean diastolic blood pressure of patients using vitamin D supplementation (M = 82.90, SD 12.28, N = 125) was not significantly different from those without vitamin D supplementation (M = 82.91, SD 11.22, N = 135) t(258) = -2.84, p = 0.565). A 95% confidence interval on the difference between the two population means using a Student's t distribution with 258 degrees of freedom is [-2.84, 2.90], which denotes that there is not significant evidence that a vitamin D supplement impacts DBPs in this study population.

An evaluation of the linear relationship between supplementation and DBP was measured using Pearson's correlation. An analysis using Pearson's correlation coefficient indicated that there was a small and non-significant linear relationship between vitamin D supplementation and DBP, r(258) = -0.001, p = 0.98. For these data, the mean (SD) for DBP was 82.90 (11.72) and for Supplement was 0.48 (0.50).

To probe deeper into the possible effects of vitamin D supplementation on blood pressures, the supplementation variable was recoded into the various dosages as previously described. When examining the various dosages of vitamin D, does this have an affect on the diastolic blood pressure? A one-way ANOVA was performed to examine diastolic blood pressure and the vitamin D dosage. The average diastolic blood pressures were found to be similar across methods $F(4, 255)$, $p = .81$. The Tukey multiple comparisons performed at the 0.05 significance level found that the mean diastolic blood pressure without supplementation was not significantly different across the treatment groups. The mean diastolic blood pressure for the no supplements group had a mean of 82.91 with a SD of 11.22. The lowest DBP was in the 4K dosage group ($M = 76$, SD 12.26, $N = 8$) and the highest DBP was in the 2K dosage group ($M = 84.74$, SD 12.02, $N = 46$). Mean diastolic blood pressures with varying dosages of vitamin D supplementation were not found to be significantly different from each other.

Chapter Five

Outcomes of Research

Chronic kidney disease (CKD) affects over 30 million people, or approximately one out of every seven Americans and continues to rise every year (CDC, 2017). The increasing frequency of CKD in the population has caused it to be one of the predictors for the incidence of cardiovascular disease and associated mortality. When comparing individuals with CKD to the general population, those with CKD have a significantly higher frequency of vitamin D deficiency (Lishmanov et al., 2013). It is hypothesized that the reduced serum 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 is linked to hypertension and endothelial dysfunction (Lishmanov et al., 2013).

This retrospective observational study was conducted on individuals from a local nephrology office explored the hypothesis of vitamin D supplementation having a positive impact on blood pressures. A total of 260 individuals were examined to determine if vitamin D supplementation versus no supplementation improved the systolic and diastolic blood pressures in this population. Upon investigation, statistical testing revealed no statistically significant improvement in systolic or diastolic blood pressures in those taking a vitamin D supplement when compared to those without supplementation.

Systolic Blood Pressure

Did the systolic blood pressure (SBP) improve in those taking a vitamin D supplementation? The data did not show a statistically significant difference in SBP when compared to those not taking supplementation. Interestingly, when examining the data, the mean SBP was three points lower in the group who did not take vitamin D

supplementation (*M* = 139.72 versus *M* = 136.67). This small difference in the SBP in those taking a supplement versus not taking a supplement was a surprising finding. This small disparity could be a result of an unknown, or one of many confounding variables, such as the individual's BMI. It is recognized that there is decreased bioactivity of vitamin D in those who are obese and they may require higher doses of vitamin D supplementation to improve cardiovascular health (Manson et al., 2019).

The next area to examine was to uncover a potential relationship between vitamin D supplementation and the systolic blood pressures. Is there an association between vitamin D supplements and the SBP? When examining the data, there was a small, but non-significant linear relationship between the SBP and vitamin D supplementation. Although statistically insignificant, there is a small positive relationship for those taking the vitamin D supplementation.

Looking deeper, the participant's usage of vitamin D was further refined to identify the specific amounts of daily supplementation. The dosages were classified as: a) Up to 1K, b) Up to 2K, c) Up to 3K, d) Up to 4K, and e) over 5K. With this reclassification, does the dosage of vitamin D supplementation have an impact on the SBP? Those identified as having the highest SBPs were found in the group utilizing the 2K dosage of vitamin D. Those with the lowest SBPs were those in the 4K dosage group. Overall, the mean SBPs, with the varying dosages of vitamin D supplement, were not found to be statistically different from each other.

Diastolic Blood Pressure

Did the diastolic blood pressure (DBP) improve in those taking a vitamin D supplement? Like the SBPs, the DBPs did not show a statistically significant difference when compared to those not taking supplementation. Unlike the SBP, the DBP means between the groups were not different (M = 82.90 versus M = 82.91).

The data were examined to assess for a relationship between vitamin D supplementation and DBP. There was a slight negative association with the DBPs and no supplementation. Generally, the DBPs and supplementation did not show a statistically significant association.

The vitamin D supplementation was divided into five categories of dosages as described earlier. Similarly, as in the SBPs, the DBPs were lowest in the 4K groups, and highest within the 2K dosage groups. Again, largely, when looking at the various dosages of vitamin D and the DBPs, there was not a statistically significant difference between the groups.

The preceding values were not statistically different from one another, but it is interesting that the highest DBPs were seen in the vitamin D dosage of 2K and not in the group of no supplementation. Also, the lowest DBPs were seen in the 4K groups, and not in the higher dosages. This is also seen in the previously discussed SBPs, when looking at the 2K and 4K groups, as opposed to the no supplementation group and higher dosage groups. Could this be a result of confounding variables such as outdoor activities and potential exposure to sunlight while taking vitamin D supplementation? Another confounding variable could be the timing of the nephrology referral and the stage of CKD when supplementation was initiated, if initiated.

Comparison to Previous Studies

Vitamin D and the effects upon cardiovascular health in those with kidney disease was previously examined in a meta-analysis in 2018 by Kaur, Singh, and Kumar. The analysis explored 20 studies of various strengths of evidence, and determined there was an improvement in cardiovascular health, namely an improvement in SBP and DBP (Kaur, Singh, & Kumar, 2018). The OIVEH study examined the SBP and DBP in those with CKD and did not find that supplementation improved either of the outcomes. The data obtained from this scholarly project is inline with larger experimental trials examining vitamin D supplementation and their respective systemic endpoints.

The VITamin D and omega-3 triaL (VITAL) study is the largest, and most recent, study to date that examines vitamin D supplementation and its effect on cardiovascular disease. The VITAL study was a randomized, placebo-controlled trial, with a two-by-two factoral design, of vitamin D at a dose of 2000 IU per day for the prevention of cardiovascular disease. The total number of participants was 25,871 and the median follow up period was 5.3 years (Manson et al., 2019). The cardiovascular disease endpoint included myocardial infarction, stroke, coronary revascularization, and death. The supplementation with vitamin D did not result in a lower incidence of cardiovascular disease than placebo (Manson et al. 2019). The VITAL study's measured outcomes support older experimental studies, such as the ViDA study.

The Vitamin D Assessment (ViDA) study was a randomized, double-blind, placebo controlled trial to evaluate the effectiveness of monthly vitamin D supplementation in reducing the occurrence of acute and chronic diseases. The ViDA study had 5110 participants and was followed for a median of 3.3 years. The intervention

was 100,000 IU or a placebo on a monthly basis. The conclusion of the study was that there was no benefit of vitamin D supplementation on the incidence of cardiovascular disease (Scragg, 2019).

Overall, the OIVEH study did not examine systemic endpoints, such as myocardial infarction or death, as seen in the VITAL or ViDA studies, but did examine specific constituents of cardiovascular health or disease, namely the SBP and DBP. More specifically, the OIVEH study examined the SBP and DBP in those with CKD to see if vitamin D supplementation had an effect on them. As documented previously, there was not a statistically significant improvement in the SBP or DBP in those taking a vitamin D supplement, and can be viewed as supporting the aforementioned experimental studies.

Reflection on Advancing Nursing Knowledge

Nurses have ideas and hypotheses pertaining to improving nursing care and contributing to the nursing body of knowledge. To adhere to the scientific principles that underpin our profession, we as professional nurses must test these ideas and hypotheses and gain the necessary evidence prior to implementation. In short, the knowledge that is added to the nursing profession comes as a result of experiential and non-experimental nursing research.

Prior medical research examined systemic endpoints such as cardiovascular disease or the prevention of cancer. Few studies have examined the finer mechanisms identified as contributing to cardiovascular disease, such as hypertension, and the potential mediating factor, vitamin D. The OIVEH study is a nurse driven research endeavor to apply previous research concepts and hypotheses to a specific sub-population, people with CKD, whose disease process can be as a result of hypertension

and can produce hypertension.

Those with CKD can have a severely limited availability of vitamin D, thereby potentially exacerbating hypertension leading to a decline in renal and cardiovascular health. The OIVEH study is a single observer nursing research project that examined data from 260 individuals with CKD and found that vitamin D supplementation did not improve the systolic or diastolic blood pressures when compared to no supplementation. This research will supplement the expanding knowledge base and provide data for the evidence based advanced nursing practice.

OIVEH Observations

Two interesting observations were seen in this study. One, the highest blood pressures were seen in those taking a vitamin D supplement. Two, the lowest blood pressures were identified in those taking, what can be considered, a mid-range dose of vitamin D. Conventional wisdom would assume that the group not taking a supplement would have the highest blood pressures, while those taking the highest doses of vitamin D would potentially have the lowest blood pressures, but this is not what the data provides.

First, why did the highest blood pressures occur in those taking a supplement versus no supplement? One hypothesis is that those individuals could be new consults or patients to the nephrology practice, therefore not having expert medical management of the blood pressure or evaluation of secondary renal processes such as conversion of vitamin D. Second, why are the lowest blood pressures seen in the mid-level dosages of vitamin supplementation? This may be influenced by one of myriad confounding variables such as BMI or how much sunlight the individuals are exposed to on a regular

basis.

Identification of the multiple potential confounding variables was one of the interesting learning experiences. These variables include parathyroid hormone levels, area of residence, exercise history, outdoor activities, adiposity, cutaneous melatonin content, and the timing of the referral to a nephrologist. The recognition of the confounding variables can lay the groundwork for continuing the OIVEH research project.

The instrument utilized to identify potential participants (Saama) functioned as designed and 260 individuals were randomly chosen for examination. The consensus of this study corroborates earlier data on vitamin D's effects on cardiovascular health, but the study design hints at need for further refinement. It was initially determined that in order to have sufficient statistical power there would be a need for at least 260 participants. Once the study was underway, it was determined that there was a need to separate the dosages of vitamin D when looking at the potential impact on blood pressures. This separation would necessitate the need to have at least 260 participants in each vitamin D supplementation group in order to gain sufficient power. This would change the number of needed participants to 1300.

Study Limitations

The largest potential limitation to this study is the nature of the study itself, a single observer, or researcher. Although there was collaboration between members of the nephrology practice, the University, and the researcher, it is understood that potential bias and error may be a restraining factor. A potential issue, that is an offshoot of the solitary researcher, is the topic of data entry. Only one person entered the data into the

spreadsheet and again into the SPSS program for analysis. Even though care was taken when entering data there exists the potential for inaccurate recording of any of the variables under scrutiny. This, in turn, can affect the statistical results obtained. This issue could be mediated by the inclusion of a secondary researcher, or a secondary research participant to examine for data integrity.

The next potential limitation to this study was time and monetary resources. The study was designed in a way to achieve completion within a few short semesters in the doctorate program. This accelerated pace can lend itself to the aforementioned limitations. Further, the identification of monetary resources such as a grant may be realized with a longer time schedule. The ability to pay an individual offers a strong incentive and can potentially secure the assistance of a secondary researcher or research assistant.

Future Research

The next steps for future research would be to expand this study to include the previously mentioned confounding variables. One example of a confounding variable that would benefit from further research would be to determine if Black individuals with CKD need a higher dosage of vitamin D supplementation than their counterparts in order to achieve a normal serum 25-hydroxyvitamin D level. Others areas to be considered could involve examining individuals with CKD living above the 30th parallel, or the amount of environmental exposure to sunlight. To further delve into the area of vitamin D supplementation the examination of the two different types of supplementation may be warranted, i.e. ergocalciferol versus cholecalciferol.

Numerous potential avenues can be considered for continuing research. As a

result of the experience gained through this research project some areas will need to be redesigned or refined. This may include evolving the research into an experimental design, or refining the current study design and applying it to a different sample population.

Design Improvement for Future Research

The improvement in design would be the use of experimentation in regards to the use of vitamin D supplementation and its effects on blood pressures. This redesign would be more labor intensive and would necessitate a much longer time frame for study. Despite the magnitude of work involved, this research design is considered to be the gold standard in terms of generating trustworthy evidence concerning cause and effect (Polit & Beck, 2012).

A brief description of an example would be that the number of study participants needed would remain the same, i.e. at least 260 per supplement group, and include those not currently on supplementation and those currently taking supplementation. Those on supplementation would go through a washout period prior to study initiation. The individuals would be randomized to each of the groups including a no supplementation group, but these individuals will be given a placebo. Serum vitamin D levels and blood pressures would be obtained at times to be determined. This type of experimental study, plus taking into account the confounding variables identified in the current study data, may shed additional light on the potential cause and effect vitamin D may have on blood pressures in those with CKD.

Additional Knowledge for Future Research

The identification of the confounding variables is one step in the accumulation of

additional knowledge. To examine these varying concepts the researcher may institute the use of a questionnaire in order to gain insight. Taking the environmental aspect of sunlight exposure, the investigator may ask a series of questions designed around the type of employment, articles of clothing worn, the amount of time spent outside, the times of day in the outdoors, any type of hobby spent in the outdoors, and the use of sunscreen when exposed to sunlight.

Implications for the Advanced Practice Nurse

The many professions, such as medicine, are grounded in scientific and mathematical evidence in order to dispel traditions and biasness, as well as, unsupported methods of practice. Research continues to consistently improve decision-making and improve patient outcomes. The nursing profession, as a whole, is not unlike any other of the sciences. The knowledge gained through research is the only means by which the nursing profession, and ultimately the advanced practice nurse will progress.

Previous information and research described within this scholarly paper has identified potential areas whereby the advanced practice nurse may use an unsupported method of practice in order to treat hypertension, such as the use of vitamin D supplementation. This potentially flawed practice may come as a result of logical fallacies or via cognitive bias. Although the process of thinking in logical and rational ways may be appropriate in most instances, it is the issue of biasness, which may be identified as a contributor to mediocre patient outcomes. This study was designed to build upon previous studies, which examined systemic endpoints, such as myocardial infarction or cancer; and sought examine a more precise endpoint, i.e. blood pressure.

Many studies described the potential benefit of vitamin D supplementation in a myriad of different arenas, such as cardiovascular disease, immunology, and oncology, to name but a few. There is a biologic plausibility for the use of vitamin D supplementation in mediating many disease processes, but much of the evidence is not statistically significant. This is true for previous research and this scholarly project. The data obtained as a result of this study will help to add to the growing body of information and evidence for advanced practice nurses. As a result, the data to be disseminated will be that vitamin D supplementation should not be construed as a means for treatment of hypertension.

Conclusion

Vitamin D is a fat-soluble hormone with specific receptor sites on almost every cell in the human body. This fat-soluble hormone has been implicated in bone metabolism, endocrine function, oncological processes, cardiovascular health through suppression of the RAAS, and all-cause mortality. Vitamin D is the only substance, which can be directly synthesized by the human body. This is carried out by the cutaneous synthesis via ultraviolet light exposure to produce 25-hydroxyvitamin D3, which is then transported to the renal tubules to form 1,25 dihydroxyvitamin D3. A vitamin D deficiency can be a result, or combination, of reduced sunlight exposure, decreased ingestion of fortified foods, and decreased renal synthesis. It is hypothesized that a vitamin D deficiency is a component to hypertension, and thus be a mediating factor. Therefore, does vitamin D supplementation, compared to no supplementation, improve the systolic and diastolic blood pressures in those with CKD? This scholarly project was designed as a retrospective observational study that examined 260 individuals with CKD stages 1 – 5 to ascertain if supplementation with vitamin D improved blood

pressures. The data obtained does not offer statistically significant evidence to support the use of vitamin D as a means to improve the blood pressures in those with CKD. It is the recommendation of this scholarly project that vitamin D supplementation should be reserved for treating a vitamin D deficiency.

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Appendix A: EOP SLO Synthesis

Cultural Competence

The act of cultural competency can be defined as a set of mindsets and actions that promote helpful and useful interactions with various cultures. Hypertension affects minorities at a higher rate than their Caucasian counterparts. This project aims to identify a potential source of mediation of hypertension. The use of vitamin D to lessen the effects of hypertension could potentially improve the care delivered to minority individuals and lessen disparities.

Evidence Based Practice

This project will utilize data from chronic kidney disease patient's health information. This data will be utilized to determine whether there is or is not a statistical likelihood of the improvement of the systolic and diastolic blood pressures with vitamin D supplementation. Although there is the potential that the data will not support my hypothesis there is a chance that the research conducted will provide a pathway, or offer more data, to warrant continued research.

Health Promotion

The supplementation of vitamin D with over-the-counter preparations is the view of this potential study. In the processes of research it has been determined that vitamin D supplementation can be successfully completed with the simple act of exposing the skin of the arms to sunlight for 10-15 minutes three times per week. Although exercise and sun exposure is not the focus of this study, and is likely a confounding factor, and these identified variables may provide information for further research.

Patient Centered Care

This scholarly project examined patient specific data to make recommendations. These recommendations have the potential to improve an individual's quality of life. One instance of improving quality of life would be the mitigation of unwanted side effects of various anti-hypertensive agents. If the supplementation of vitamin D can improve the systolic and diastolic blood pressures then there is a possibility of reducing or eliminating the medications, thereby removing the potential for side effects and improve a person's quality of life. Unfortunately, the outcomes of this study do not support the use of vitamin D in the realm of blood pressure management. As a result, to improve patient centered care utilizing evidence-based research the recommendation of this project is to use vitamin D supplementation to treat a vitamin D deficiency.

Quality and Safety

The concept of quality was maintained by eliciting the assistance of the physician's research group in gathering the required data. A potential safety issue included potential HIPPA violations. These potential violations were mediated through the elimination of private health information. The participants chosen were assigned a random number with their respective ages and racial category. The dates of birth, addresses, social security numbers, and patient identification numbers were not utilized, nor catalogued. Data acquisition took place utilizing an encrypted application and was carried out in secure locations. The data gathered was archived onto a single USB memory drive dedicated for this scholarly project.

Informatics and Innovation

The electronic medical records of Nephrology Associates was queried to obtain the necessary data using Saama and NextGen. The utilization of these software applications eliminated the potential tedious task of reviewing outdated medical record keeping practices, such as handwritten notes. After gathering the necessary data, the data was analyzed and interpreted via the SPSS statistical software program.

Teamwork and Collaboration

This scholarly project has enlisted the assistance of two Southern Adventist University professors, two physician researchers, and one research director. The communication that was required has been substantial, but necessary. Dr. Brett Jennings, the research director, was instrumental in getting this project underway. Dr. Jennings set the parameters within the program, Saama, utilizing the inclusion and exclusion criteria in order to obtain the necessary number of participants.

Professionalism

It is the belief of this researcher that professionalism has been maintained during the course of this project. I have maintained open communication with the physician researchers and research director. I have also communicated the intention of not impressing upon research time that is dedicated to Nephrology Associates' programs already in progress. I have implemented and maintained a flexible timeline. I have utilized the timeframe set about in the previous semester's work, and have updated it to highlight due dates. All of these strategies were in hopes to maintain professional working relationships.

Appendix B: IRB

FORM A
Not required for a literature review/academic exercise.
RESEARCH APPROVAL

Research Request: ____Exempt __X__Expedited ____Full Review ____Other (Animal/Plant)

This box is for SAU – IRB Office Use Only

IRB Tracking #_____

Date Received _____ _____Exempt _____Expedite ____Full Review ____Other (Animal/Plant)

1) IRB Board Approver _____ _____ _____
Name Title Date

2) IRB Board Approver _____ _____ _____
Name Title Date

Date Approval Sent_____

Title of Research Project: Examining the Role of Vitamin D Supplementation on Hypertension _____

Principal Investigator: Warren Burke	E-mail Address: wburke@southern.edu
	Phone #: 423-650-8960
Co-Investigator:	E-mail Address:
	Phone #
Co-Investigator:	E-mail Address:
	Phone #:
Co-Investigator	E-mail Address:
	Phone #:
Department: Nursing	Faculty Supervisor: Dr. Frances Johnson
Starting Date: 5/01/2019	Estimated Completion Date: 5/01/2020
Cooperating Institutions: Is this research being done with any institutions, individuals or organizations not affiliated with SAU? If yes, please provide the names and contact information of authorized officials below.	
Name of Institution	Address:
Contact Name:	Phone #:
Contact E-mail:	
External Funding Agency: N/A	Identification # (if applicable)
Grant Submission Deadline (if any)	

Please attach all of the following items, making sure the entire application is completely filled out (where applicable) before submitting the application:

- Any research instruments (tests, surveys, questionnaires, protocols, or any form else used to collect data)
- All informed consent documents

- Permission from applicable authorities (principals of schools, teachers of classrooms, etc.) to conduct your research at their facilities on their School Letterhead.
- Students need signatures from their faculty advisor.

All student applications must be signed by the faculty advisor then scanned and submitted electronically, or submitted directly by the faculty advisor. All applications should be submitted by email to irb@southern.edu.

Please be aware you cannot begin your research until it has been officially approved by the IRB.

Type of Research- Check all areas that apply

____ Dissertation/Thesis

____ Funded Faculty Research

____ General Faculty Research

____ Applying for ARC Funding

__X__ Student Research

____ Other: Animal/Plant

Background and Rationale for the Study: (This section should present the context of the work by explaining the relation of the proposed research to previous investigations in the field. Include citations for relevant research.)

In the United States, the prevalence of Chronic Kidney Disease (CKD) in individuals over the age of 30 has reached over 13%, and is expected to increase to over 14% by 2020, and rise to 17% by 2030 (Hoerger, Simpson, Yarnoff, Pavkov, Rios, Saydeh, et al., 2015). The chronicity of the disease leads to other health issues and includes, but is not limited to anemia, metabolic derangements, worsening of cardiovascular disease, and vitamin D deficiency. CKD, and the inevitability of these complications, causes a tremendous burden on the American healthcare system and its' resources. In 2015 alone the total cost for CKD, which included end stage renal disease (ESRD), was over $98 billion Medicare dollars (United States Renal Data System, 2017).

One complication, Vitamin D deficiency, is almost ubiquitous in the ESRD population, and affects upwards of 80% of the pre-dialysis CKD population (Caravaca-Fontan, Gonzales-Candia, Luna, & Caravaca, 2016). Chronic kidney disease (CKD) affects over 30 million Americans, or 15% of the population. One out of every seven American adults is thought to have chronic kidney disease, and one in three are at risk (CDC, 2017). The increasing frequency of CKD in the population has caused it to be one of the predictors for the incidence of cardiovascular disease and associated mortality. Further, when comparing individuals with CKD to the general population, those with CKD have a significantly higher frequency of vitamin D deficiency (Lishmanov et al., 2013). The higher incidence of this deficiency is linked to reduced vitamin D fortified food intake and lessened cutaneous synthesis via skin exposure to UV-B radiation. As a result, the deficiency of the precursors (ergocalciferol and cholecalciferol) plus

the reduced renal mass seen in those with CKD causes the severe reduction in the conversion of 25-hydroxyvitamin D3 (cholecalciferol) to 1,25-dihydroxyvitamin D3 (calcitriol). As a result, it is theorized that the reduced serum 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 is linked to hypertension and endothelial dysfunction.

Purpose/Objectives of the Research: (Briefly state, in non-technical language, the purpose of the research and the problem to be investigated. When possible, state specific hypotheses to be tested or specific research questions to be answered. For pilot or exploratory studies, discuss the way in which the information obtained will be used in future studies so that the long-term benefits can be assessed.)

In the individual with CKD, does vitamin D supplementation, compared to no supplementation, improve the systolic and diastolic blood pressures? The researcher proposes a retrospective observational study to determine the effects of vitamin D on individuals with hypertension.

Methods and/or Procedures: **(**Briefly discuss, in non-technical language, the research methods which directly involve use of human subjects. Discuss how the methods employed will allow the investigator to address his/her hypotheses and/or research question(s).)

The proposed non-experimental retrospective observational study will be used to find if vitamin D supplementation, compared to no supplementation, improves the systolic and diastolic blood pressures.

The patient data to be examined are to be obtained from Nephrology Associates. The prospective subjects will be obtained from the Nephrology Associates' electronic medical record (EMR) database of over 10,000 active CKD patients. A software program, identified as NextGen, will be utilized in order to select prospective patients based on inclusion and exclusion criteria can query the EMR. The proposed data mining, within medical records, can present a risk for private heath information to be exposed causing potential HIPPA violations. To this end, steps will be taken to negate the possible breech of privacy. All patient identifiers will be removed and replaced with a single identifying number for this proposed study

The inclusion criteria include a diagnosis of CKD stage I through IV(per current guidelines and definitions), along with a diagnosis of hypertension, are on at least one anti-hypertensive agent, are between the ages of 21-60, and have a systolic and diastolic blood pressure reading with a concurrent serum cholecalciferol level at the time of follow up.

The exclusion criteria will those who do not have a diagnosis of hypertension, those who take an angiotension converting enzyme inhibitor (ACEI) or an angiotension receptor blocker (ARB) for proteinuria without a diagnosis of hypertension, those with a diagnosis of medical non-compliance with an ICD-10 code of Z91.1, those under the age of 21, the terminally ill, the mentally incompetent, pregnant individuals, those with a diagnosis of sarcoidosis, an active malignancy, or an active thyroid disease.

Permission and clearance to observe patient data for this proposed scholarly project has been obtained from Nephrology Associates. Nephrology Associates is a private nephrology practice comprising of fifteen physicians, and ten nurse practitioners serving the Southeast Tennessee and North Georgia areas. Assistance will be obtained from the Southeast Renal Research Institute, a division of Nephrology Associates based in Chattanooga, Tennessee.

Analysis:

This proposed study will utilize a moderate effect size of .50, and a power of .80 (Polit & Beck, 2012). The needed sample size for this observational study will be 256 patient records, categorized into four groups

1. HTN with low serum Vit D
2. HTN with normal Vit D
3. Normal BP and low serum Vit D
4. Normal BP and normal serum Vit D

The total N is based on the Cohen table for two-tailed testing (Polit & Beck, 2012). The groups will be examined using either the one-way ANOVA or the Kruskal-Wallis, if the assumptions for the ANOVA are not met.

The null hypothesis is that there will be no difference in serum cholecalciferol levels and hypertension, while the alternate hypothesis will be that a normal serum cholecalciferol level will correlate to controlled hypertension.

The project will utilize the Pearson r correlation to measure the strength of association between the variables of hypertension and serum cholecalciferol. These previous statistical tests are what is projected to be needed or utilized. Based on previous experimental and non-experimental study data, it is theorized that the data will be different among the groups.

Description of Research Sample: If human subjects are involved, please check all that apply:

____ Minors (if minors are involved please attach a Childs Assent Form)
____ Prison Inmates
____ Mentally Impaired
____ Physically Disabled
____ Institutionalized Residents
____ Anyone unable to make informed decisions about participation
____ Vulnerable or at-risk groups, e.g. poverty, pregnant women, substance abuse population
____ Health Care Data Information - be sure to attach any necessary HIPAA forms if this line is checked
____ Other: Animals or plants will be used
__X__ **Other: Patient Data from Nephrology Associates**

Approximate Number of Subjects: ___256___

Participant Recruitment:
Describe how participant recruitment will be performed. Include how potential participants are introduced to the study (Please check all that apply)

SAU Directory:	Postings, Flyers	Radio, TV
E-Mail Solicitation	How Were Addresses Obtained	
Web-based Solicitation	Indicate Site	Indicate Site
Participant Pool	What Pool	
Other, Please Specify: Random selection using the Electronic Medical Record for Nephrology Associates		
Attach Any Recruiting Materials You Plan to Use and the Text of E-mail or Web-based Solicitations You Will Use		

Content Sensitivity:
Does your research address culturally or morally sensitive issues? ___Yes __X__ No If yes, please describe.

Privacy and Confidentiality:
Efforts will be made to keep personal information confidential. We cannot guarantee absolute confidentiality. Personal information may be disclosed if required by law. Identities will be help in confidence in reports in which the study may be published and databases in which results may be stored.

Will personal identifiers be collected? ___ Yes __X__ No
Will identifiers be translated to a code? __X__ Yes ___ No
Will recordings be made (audio, video) ___ Yes __X__ No If yes, please describe.

Is Funding being sought to support this research? ___N____

Circle to indicate if the funding is: Internal or External Funding? Is there a funding risk? ___N_____

Who will keep the financial records?
___N/A_____

Who will have access to data (survey, questionnaires, recordings, interview records, etc.)? Please list below.

- Warren Burke, Student Researcher
- Dr. Frances Johnson, Primary Faculty Advisor
- Dr. Mike Liedke, Faculty Advisor
- Dr. Mandeep Grewal, Medical Director for Nephrology Associates
- Dr. Brett Jennings, Director of the Southeast Renal Research Institute
- Dr. Claude Galphin, Principle Investigator for Nephrology Associates and the Southeast Renal Research Institute

- Statistician
- Southeast Renal Research Institute

Participant Compensation and Costs

Are participants to be compensated for the study? ____ Yes __N__ No
If yes, what is the amount, type and source of funds:
Amount $____N/A_____ Type:_____N/A_____ Source _____N/A_____

Will participants who are students be offered class credit? ____ Yes __X__ No ____ NA
Are other inducements planned to recruit participants? ____ Yes __X__ No If yes, please describe
Are there any costs to participants? ____ Yes __X__ No If yes, please explain _____

Other: Animals/Plants

Are the animals/plants being studied on the endangered list? ____N/A_____

Are Scientific Collection Permits required, i.e. Tennessee Wildlife Resources Agency? ____N_____

Have the animal(s) utilized in this study already been used in a previous study (non-naïve animals)? ___N/A____

Will the animal(s) used in this study be used in a future study? ___N____

Where will the animals be housed? ____N/A_____

Will the rodents (if applicable) be housed in wire bottom cages? ___N/A___

Will plants be used for instructional purposes as part of teaching a course? ____N_____

Are there any risks involved with this study? ___X__Yes _____No

Are there any potential damage or adverse consequences to researcher, participants, or environment? These might include physical, psychological, social, or spiritual risks whether as part of the protocol or a remote possibility. Please indicate all that apply.

_____ **Physical Risk:** May include pain injury, and impairment of a sense such as touch or sight. These risks may be brief or extended, temporary or permanent, occur during participation in the research or arise after.

____ **Psychological Risk:** Can include anxiety, sadness, regret and emotional distress, among others. Psychological risks exist in many different types of research in addition to behavioral studies.

____ **Social Risk:** Can exist whenever there is the possibility that participating in research or the revelation of data collected by investigators in the course of the research, if disclosed to individuals or entities outside of the research, could negatively impact others' perceptions of the participant. Social risks can range from jeopardizing the individual's reputation and social standing, to placing the individual at-risk of political or social reprisals.

__X__ **Legal Risk:** Include the exposure of activities of a research subject "that could reasonable place the subjects at risk of criminal or civil liability".

The legal risks are related to potential HIPPA violations. These potential violations will be mediated through the elimination of private health information. The participants, who are chosen, will be assigned a random number with their respective ages and racial category. The dates of birth, addresses, social security numbers, and patient identification numbers will not be utilized, nor catalogued. Once data acquisition begins, this work will only take place in a single and secure location. This location will be Nephrology Associate's Research Institute's offices, where dedicated computers utilize the corporation's electronic medical record systems of Cerner and NextGen. The data gathered will be archived onto a single USB memory drive dedicated for this scholarly project. Those privy to the raw data have been listed previously in this application.

____ **Economic Risk:** May exist if knowledge of one's participation in research, for example, could make it difficult for a research participant to retain a job or find a job, or if insurance premiums increase or loss of insurance is a result of the disclosure of research data.

____ **Spiritual Risk:** May exist if knowledge of one's spiritual beliefs or lack of, could be exposed which in turn could invoke an economic, social and or psychological risk.

Risks: In your opinion, do benefits outweigh risks? __X__ Yes ____ No

Results:

The results will be disseminated as:
_____Classwork only _____Student conference _____ Professional conference
___X___Published article _____Other If other, please specify: _X_DNP Scholarly Project_

Signatures: If submitted by a faculty member, electronic (typed) signatures are acceptable. If submitted by a student, please print out completed form, obtain the faculty advisor's signature, scan completed form, and submit it via e-mail. Only Word documents or PDF files are acceptable submissions.

Principal Investigator (PI) or Student	**Date**
Faculty Advisor (for student applications)	**Date**

All student applications must be signed by the faculty advisor then scanned and submitted electronically, or submitted directly by the faculty advisor. All applications should be submitted by email to: irb@southern.edu

Additional Special Requirements or Attachments to the Application

Approvals from other IRBs

Cooperative research projects involve research that involves more than one institution. In these instances, federal law holds each institution responsible for safeguarding the rights and welfare of human subjects and for complying with federal policy; therefore, SAU IRB applications must be made even if there is another institution conducting a review of the same research project. When a study is being carried out at a non-USA site, and approval from other institutional review boards at the foreign site must be sought. The IRB recommends that a copy of each IRB approval be submitted.

Questionnaires/Other Instruments

Any questionnaires, tests, survey instruments or data collections sheets which are not standard and well known must be submitted as part of the application. Structured interview questions and outlines for unstructured interviews also must be included.

A spreadsheet in SPSS will be utilized to catalogue the data. There are no questionnaires, tests, or surveys to be completed for this proposed study.

Advertisements/Notices/Recruitment Flyers

The text of any advertisement, video display, notice, sign, brochure or flyer used to recruit subjects either should be included as an attachment.

There are no advertisements, video displays, notices, signs, or brochures to be utilized to recruit subjects in this proposed study.

Appendix C: IRB Approval

April 29th, 2019
Principal Investigator: Warren Burke
Research Project: Examining the Role of Vitamin D Supplementation on Hypertension
IRB Tracking Number: 2018-2019-078
Dear Warren,
It is a delight to inform you that the Institutional Review Board examined your research study proposal and supporting documents and the IRB committee has approved your research request as **expedited.** We wish you the very best as you move forward with this study and look forward to reading your findings when they are ready.
If there are minor changes to this research, before making those changes please notify us by completing and submitting FORM B (Certification of Modification, Annual Review, Research Termination, or Research Completion). Please submit applications to irb@southern.edu. If substantial changes are planned you, as the principal investigator, should submit a new IRB FORM A application.
Many blessing to you as you move forward. Please let us know if there is anything else we can do to assist you with this research study.
Always in His service,

Cynthia
Cynthia Gettys, Ph.D.
IRB Chair
Southern Adventist University
423-236-2285
cgettys@southern.edu

"I applied my mind to **study** and to explore by wisdom all that is done under the heavens…" - Ecclesiastes 2:13
"Research is to see what everyone else has seen and to think what nobody else has through." - Albert Szent-Gyorgyi